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IDENTITY OF SPRUE, NONTROPICAL SPRUE AND CELIAC DISEASE

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The syndrome which will be discussed in this paper has acquired many names during its curious history. The term "sprouw" was first used by Vincent Ketelaer [1] in 1669 in his description of an aphthous stomatitis occurring among the Belgians and associated with feces so copious "that several basins or pots scarcely hold these accumulations." William Hillary [2] is usually credited with the first description of the sprue syndrome, which he observed in the Barbados in about 1754, but the clearest modern reports were those by Manson, in China, and by Van der Burgh, in Java, both of which were published in 1880.

The disease soon became known as "tropical sprue," an unfortunate designation since it has contributed to the erroneous impression that sprue does not occur in temperate climates. For many years, however, sprue has been known to be endemic in North Carolina and Virgina, and from the states farther south many cases have been recorded. Snell [3] stated that more than a hundred cases of sprue occurring in temperate climates are on record, and one may safely presume that many more have gone unrecognized. The disease has frequently been confused with pellagra, an error which Edward Jenner Wood [4] clearly pointed out twenty years ago, and, from the experience of our own

From the Departments of Medicine and Pediatrics, Duke University School of Medicine.

1. Ketelaer, Vincent, cited by Major, R. H.: Classic Descriptions of Disease, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

2. Hillary, William, cited by Major, R. H.: Classic Descriptions of Disease, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

3. Snell, A. M.: Clinical Observations on Nontropical Sprue, South. M. J. **28**:516, 1935.

4. Wood, E. J.: The Occurrence of Sprue in the United States, Am. J. M. Sc. **150**:692, 1915.

clinic we are convinced that many of the disorders that have been described as pernicious anemia with free hydrochloric acid in the gastric juice are instances of the sprue syndrome. When sprue was found to occur in temperate climates, it was termed "nontropical sprue," and more recently the term "idiopathic steatorrhea" has been coined for the syndrome, to distinguish it from pancreatogenous and other steatorrheas.

Gee in 1888 [5] gave a brief but good description of a curious wasting disease of children which he termed "the coeliac disease." Herter, working with Holt in New York, published in 1908 a small monograph entitled "Intestinal Infantilism," and Heubner, in Germany, described a condition in young children called by him *"Verdauungsinsuffizienz"* or "chronic intestinal indigestion." It is now universally recognized that Gee, Herter and Heubner were describing identical syndromes under different names. We agree with Thaysen [6] that all these names are designations for the same underlying pathologic condition occurring both in adults and in children, and since the name "sprue" obviously has priority over all others, we think it best to adhere to the term "sprue" or (to broaden the conception somewhat) "the sprue syndrome." We shall present in this paper the evidence that has led us to this conclusion.

Within the past year nine patients with the sprue syndrome have come under our observation at the Duke Hospital; in two the disease began in infancy and in seven, in adult life; none of the patients has ever resided in the tropics. Since space is not available for the presentation of all the histories, only two will be given in detail; one (case 3, fig. 1) is a typical example of sprue in an adult and the second (case 5, fig. 2) is an instance of sprue which, beginning in infancy, has persisted to the age of 17, causing dwarfism. A brief synopsis of the other seven cases is given.

REPORT OF CASES

CASE 1.—A. B., a woman aged 44, the wife of a farmer residing in North Carolina, who had never lived out of the state, complained of indigestion, weakness and great loss of weight (she had lost 85 pounds [38.6 Kg.], or 50 per cent of her former weight).

Examination of the blood showed macrocytic hyperchromic anemia. The stools were not analyzed for fats. Analysis of the gastric content showed no free hydrochloric acid during fasting and 68 degrees hydrochloric acid after stimulation with alcohol and histamine. (These results were confirmed by a second analysis.) A test for dextrose tolerance showed a very flat curve, the maximum rise in the sugar content of the blood being 11 mg. per hundred cubic centimeters.

Marked and steady improvement resulted from a diet rich in proteins with the addition of liver.

5. Gee, Samuel: On the Coeliac Affection, St. Barth. Hosp. Rep. **24**:17, 1888.

6. Thaysen, T. E. H.: (*a*) Nontropical Sprue: A Study in Idiopathic Steatorrhoea, Copenhagen, Levin & Munksgaard, 1932; (*b*) La stéatorrhée idiopathique, la sprue tropicale et non tropicale et l'infantilisme intestinal, Arch. d. mal. de l'app. digestif **24**:123, 1934.

CASE 2.—M. R., a widow aged 60, had always lived on a farm in North Carolina. She complained of diarrhea of four years' duration and of weakness and loss of weight (she had lost 50 pounds [22.7 Kg.], or 40 per cent of her former weight).

Examination of the blood showed macrocytic hyperchromic anemia. The stools were bulky, frothy, unformed and fatty. Analysis of the gastric content showed no free hydrochloric acid during fasting and 36 degrees free hydrochloride acid after stimulation with alcohol and histamine. A test for dextrose tolerance showed a very flat curve, the maximum rise in the sugar content of the blood being 9 mg. per hundred cubic centimeters. There was generalized osteoporosis, the calcium content being 7.4 mg. and the phosphorus content 2.4 mg. per hundred cubic centimeters of blood.

Under liver therapy the patient gained 26 pounds (11.8 Kg.), or 36 per cent of her weight at entrance, in five months.

CASE 3.—J. M. T., a man aged 51, was admitted to the Duke Hospital on April 4, 1935, complaining of diarrhea of eighteen months' duration and great loss of weight and strength (he had lost 58 pounds [26.3 Kg.], or 37 per cent of his former weight).

The family and the past history were noncontributory.

Present Illness.—Fifteen years before, while the patient was working as the foreman of a construction gang in Louisiana, indigestion developed. The patient stated that about one-half hour after meals he began to suffer from pain in the abdomen; this was of a burning character and accompanied by eructations of gas. He had what he described as an "acid taste" in his mouth and began to have periods of diarrhea alternating with periods of constipation. The diarrhea recurred each spring and was characterized by the passage of large amounts of foul-smelling semiliquid stools without blood or mucus. He had periods of abdominal pain, especially early in the morning, which were relieved by a bowel movement. During the periods of diarrhea he lost considerable weight, but he regained it after the diarrhea had ceased. His color gradually became sallow and yellowish. His diet was composed largely of carbohydrates.

Five years before his admission to the hospital the patient returned to his home in North Carolina. He improved, and his health remained fairly good until eighteen months before admission, when the diarrhea recurred with great severity, the number of stools varying from two to ten daily. He became so weak and lost so much weight that he was no longer able to work. He suffered almost continuously from gaseous intestinal indigestion associated with the passage of enormous frothy, foul stools. During the past year his mouth had been sore and "scalded." His diet had consisted largely of milk and eggs, fruit juices, bananas and a little liver. He had grown so weak in the past few months that he had been forced to keep to his bed and had walked only with assistance. He had noticed progressive numbness of his hands and feet. He stated that when the feet were "asleep" he could not tell their position in the bed. His maximum weight was 155 pounds (70.3 Kg.), and when he entered the hospital he weighed 97 pounds (44 Kg.).

Examination (fig. 1).—The positive findings were as follows: The patient was emaciated to the "skin and bones" stage. He weighed 97 pounds (44 Kg.) and was about 5½ feet (164 cm.) in height. The skin was grapefruit colored; the tongue was red and beefy and showed marked papillary atrophy. Except for these findings the general physical examination gave negative results.

Neurologic examination revealed diminution of the ankle and knee jerks and a distinct lowering of vibratory sensation over the feet, but no other abnormalities.

The blood showed typical hyperchromic macrocytic anemia with anisocytosis and poikilocytosis. The hemoglobin content was 6.4 Gm. (41 per cent of 15.5 Gm.); the red blood cells numbered 1,650,000; the color index was 1.24; the mean corpuscular volume, 120 cubic microns; the mean corpuscular hemoglobin content, 38.7 per cent; the percentage of reticulocytes, 1 per cent; the white blood cell count, 3,900. The differential count gave normal results. The Wassermann test was negative. The calcium content of the serum was 7.6 mg. per hundred cubic centimeters; the albumin content, 2.89 Gm., and the globulin content, 1.87 Gm. The phosphorus content of the blood was 3.2 mg. per hundred cubic centimeters,

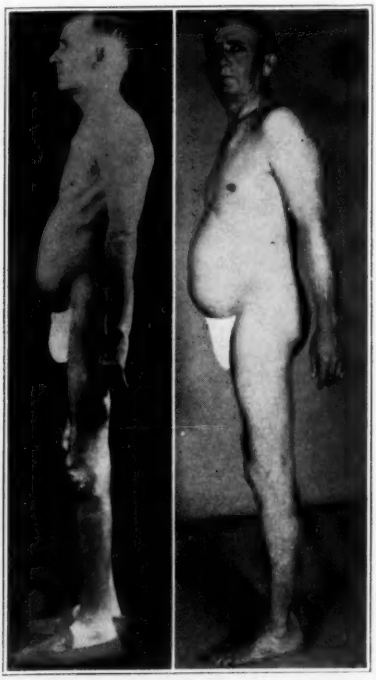

Fig. 1 (case 3).—Photographs of the patient, illustrating the effect of treatment with liver after the patient gained 15 pounds (6.8 Kg.) in thirty days and after he had received liver extract for six months.

and the cholesterol content, 150 mg. Analysis of the gastric content showed no free hydrochloric acid in the stomach during fasting, but forty-five minutes after stimulation with histamine there was observed to be 4 degrees. The basal metabolic rate was —15 per cent. Oral administration of 100 Gm. of dextrose gave a flat curve, the sugar content of the blood being 83 mg. per hundred cubic centimeters during fasting and 87 mg. one-half hour, 95 mg. one hour, 94 mg. two hours, and 88 mg. three hours, after administration of dextrose. After intravenous administration of 25 Gm. of dextrose the sugar content of the blood was as follows: during fasting, 77 mg. per hundred cubic centimeters; one-half hour after

injection, 145 mg.; one hour after injection, 103 mg.; two hours after injection, 78 mg., and three hours after injection, 77 mg. The van den Bergh test gave an indirect reaction. The bilirubin content of the serum was 0.8 mg. per hundred cubic centimeters. The icteric index was 15. Studies of the bones showed no decalcification. Roentgen examination of the gastro-intestinal tract showed no defects of the stomach or small intestines, as described by Mackie and by Snell, but marked dilatation and sluggishness of the colon were observed.

The stools were constantly large, frothy, and ill smelling, their number varying from two to eight in twenty-four hours. Examination of a twenty-four hour specimen of April 8, 1935, gave the following results: total dry matter, 7.95 per cent of the total weight (normal value, 20 per cent); total fat, 38.6 Gm., or 29 per cent of the dry matter (normal value, 17.5 per cent); free fatty acid, 28.5 Gm., or 21.4 per cent of the dry matter (normal value, 5.5 per cent); neutral fat, 6.9 Gm., or 5.2 per cent of the dry matter (normal value, 7.3 per cent); soap, 3.2 Gm., or 2.4 per cent of the dry matter (normal value, 4.6 per cent); total nitrogen, 4.6 Gm., or 3.4 per cent.

It was decided to try the therapeutic value of addisin, made after the method of Morris from the patient's own gastric juice and from the gastric juice of normal persons. In neither experiment was there any rise of the reticulocyte count worthy of note.

Course.—Six weeks after admission the patient's condition was unchanged or slightly worse. Sternal puncture revealed hypertrophic bone marrow with tremendous numbers of erythroblasts and myeloblasts. There were 25 per cent reticulated red blood cells. The picture presented by the peripheral blood had not altered, and the number of reticulocytes, which were counted daily, had never been above 2 per cent.

Liver extract was then given by mouth. This was done in order to compare the results with those produced by the ingestion of the extract in pellagra, as Dr. Smith and Dr. Ruffin of the clinic of the Duke Hospital had found this extract inefficacious in controlling the symptoms of the disease when administered orally. The patient received 120 cc. of the extract by mouth for five days.[7] Five days after this treatment was begun the reticulocyte count had risen from 0.5 to 5 per cent; eight days later it reached a maximum of 10.8 per cent, and then it gradually declined, reaching 0.1 per cent on the fourteenth day. The number of red cells, however, showed only a slight rise, the count being 1,780,000. Nevertheless, within forty-eight hours after liver extract was given the patient's general condition showed an extraordinary change for the better. His appetite became ravenous, whereas during the preceding six weeks he scarcely ate at all. He had lain in a condition of hebetude and exhaustion, sleeping much of the time, but after liver extract was administered his manner changed gradually to moderate alertness. The transformation would have been incredible had one not witnessed so often the same type of change in patients with pernicious anemia. He became very constipated, whereas before treatment he had had diarrhea and had passed frequent large, frothy, ill-smelling stools. The tongue became normal in appearance.

Twenty-nine days before the patient was discharged intramuscular administration of concentrated liver extract was begun in doses of 5 cc.; twenty-three injections were given. The patient received in addition 30 cc. daily of a crude whole liver extract by mouth and also as much liver as he could eat. His diet was otherwise unchanged from the regular ward diet; no attempt was made to exclude or emphasize any one type of foodstuff except that the patient was encouraged to

7. The liver extract was supplied by Ely Lilly & Company, Indianapolis.

eat six bananas daily. On this regimen he ate ravenously and gained 17 pounds (7.7 Kg.) in three weeks. He became jovial and said that he had not felt so well for fifteen years.

On the day of discharge an examination of the blood showed: red cells, 2,900,000; hemoglobin content, 9.8 Gm. (63 per cent of 15.5 Gm.); color index, slightly over 1; white cells, 6,200; reticulocytes, 1 per cent. The size and shape of the erythrocytes were normal, being in striking contrast to the anisocytosis and poikilocytosis seen on entry. A final gastro-intestinal roentgen study, made two days before discharge, showed nothing abnormal, except that the colon which was formerly "sluggish and dilated" now showed hypermotility. During the last month in the hospital the patient was constipated, as a rule, but he had two episodes of loose, frequent stools.

Follow-Up Note.—The patient was seen again on Oct. 26, 1935, at which time he had gained a total of 69 pounds (31.3 Kg.) since his admission to the hospital on April 3, 1935 (a gain of 70 per cent of his weight on admission). The red blood cell count was 4,710,000; the hemoglobin content, 14.3 Gm. (92 per cent), and the color index, 0.98. The patient looked the picture of health and stated that he felt "as well as ever." His only complaint was of a rare recurrence of diarrhea, which lasted for only a few hours.

CASE 4.—M. M., a girl aged 27 months, failed to gain weight and passed bulky frothy, fatty stools. Examination of the blood showed macrocytic hyperchromic anemia. The red cell count was 1,700,000; the hemoglobin content, 7.8 Gm. (50 per cent); the color index, 1.44, and the mean corpuscular volume, 147. Analysis of the gastric content showed 50 degrees of free hydrochloric acid during fasting. A test for dextrose tolerance demonstrated a flat curve, the maximum rise in the sugar content of the blood being 37 mg. per hundred cubic centimeters.

Marked improvement in every way resulted from a diet rich in proteins and vitamins, to which liver was added.

CASE 5.—J. McC., a youth aged 17, was admitted to the medical service of the Duke Hospital on June 16, 1935. He had been studied on a former admission, when he was 11 years old, in the pediatric department.

The family history was not important.

Past History.—When the patient was 18 months old he had a severe attack of dysentery, and the mother noticed that the abdomen began to enlarge. For the next two years he was weak; he walked with difficulty, and the abdomen gradually increased in size. During all this time his bowels had been loose—he had from four to eight stools daily—and severe hemorrhoids had developed. When the patient was 3 years old he was given a daily diet of one egg, eight bananas, a tablespoonful of jello, cottage cheese, cereals and four glasses of lactic acid milk. On this diet he improved for a while, but in a few months symmetrical cutaneous lesions developed, which were diagnosed as pellagra. Yeast was added to his diet, together with liver, cod liver oil and fruit juices; the cutaneous lesions disappeared, and considerable improvement in his general condition occurred. However, for the next eight years he failed to grow normally, and the diarrhea persisted, large foul stools being passed.

When the patient was 11 years of age the following diagnoses were made: celiac disease with dwarfism, secondary anemia and subsiding pellagra. It is of interest that when the patient was seen two months after discharge his anemia, which had been of a secondary type, had changed to a hyperchromic type. The red blood cells numbered 1,900,000; the hemoglobin content was 46 per cent, and the color index, 1.2.

Present Illness.—On June 19, 1935, the patient became acutely ill with fever and sharp pains in the lower portion of the abdomen. The stools became more frequent. On June 14 he experienced difficulty in voiding, and his bladder became swollen and painful. The next day he became edematous, the legs swelling first and then the body, face and arms, but this had subsided at the time of entrance.

Examination.—The patient, although 17 years of age, had the physical development of a boy of 7 years (fig. 2), being about 4 feet (120 cm.) tall and weighing 50 pounds (22.7 Kg.). The skin was dry, coarse and wrinkled; there was little subcutaneous fat, but the abdomen was huge and protuberant. The voice was high pitched and childish. The genitalia were infantile. The results of physical and neurologic examinations were otherwise normal.

Fig. 2 (case 5).—Photograph of the patient, showing dwarfism due to sprue. The patient's height was about 4 feet (120 cm.); his weight, 50 pounds (22.7 Kg.).

The blood count revealed a secondary anemia, the red cell count being 2,730,000, the color index 0.78 and the white cell count 12,000. The differential count was normal. The Wassermann test was negative. A dextrose tolerance test, 30 Gm. of dextrose being administered orally, gave a flat curve, the sugar content of the blood being as follows: during fasting, 83 mg. per hundred cubic centimeters; one-half hour after administration of dextrose, 92 mg.; one hour after administration, 85 mg.; two hours after administration, 86 mg., and three hours after admin-

istration, 75 mg. The cholesterol content was 136 mg.; the calcium content, 8.1 mg., and the phosphorus content, 4.4 mg., per hundred cubic centimeters of blood. The plasma proteins totaled 6.2 Gm. per hundred cubic centimeters—2.9 Gm. of albumin and 3.3 Gm. of globulin, a ratio of 47 : 53.

The stools were tan, voluminous, foamy and liquid for the most part and had a very foul odor. No parasites were found. There was no evidence of undigested food except for a moderate excess of fat, as revealed by staining with sudan III. Tests with benzidine and guaiac were negative. Chemical analysis of a twenty-four hour specimen of stool gave the following results: total dry matter, 39 Gm.; total fat, 44.2 Gm.; free fatty acid, 26.1 Gm.; neutral fat, 13.1 Gm.; soaps, 4.9 Gm., and nitrogen, 7.7 Gm.

Analysis of the gastric content was made. During fasting there was no free hydrochloric acid; the total acid was 6 degrees of tenth-normal sodium hydroxide. Forty-five minutes after stimulation with 0.008 Gm. of histamine the free hydrochloric acid was 50 degrees, and the total acid, 80 degrees.

The basal metabolic rate was +20.

Roentgen studies of the colon after administration of barium sulfate showed many redundant loops and elongation. The findings were consistent with megalocolon. Roentgenograms of the skeleton showed delayed epiphyseal development.

Diagnosis.—The case was regarded as an example of classic infantilism resulting from sprue. Administration of large quantities of liver, together with calcium, viosterol, iron and a high vitamin diet, was prescribed, which produced marked improvement in his condition.

Case 6.—L. J., a married woman aged 29, had lived on a farm in North Carolina all her life. She complained of diarrhea, weakness and great loss of weight (she had lost 40 pounds [18.1 Kg.], or 39 per cent, of her former weight).

Examination of the blood showed macrocytic hyperchromic anemia. Analysis of the stools gave the following results: total fats, 37.7 per cent; free fatty acids, 20 per cent; neutral fat, 6 per cent; soaps, 11.9 per cent. Analysis of the gastric content showed 5 degrees of free hydrochloric acid during fasting and 16 degrees after stimulation with histamine. A test for dextrose tolerance showed a very flat curve, the maximum rise in the sugar content of the blood being 4 mg. per hundred cubic centimeters of blood.

There was marked response to liver therapy; the patient gained 60 pounds (27.2 Kg.) in weight in sixty-six days.

Case 7.—H. H., a married woman aged 25, who had lived on a farm in North Carolina all her life, complained of diarrhea which had been present for three and one-half months. She had given birth to a child eight months before she was seen. She showed evidence of deficient nutrition.

Examination of the blood disclosed macrocytic hyperchromic anemia. The stools were copious and watery; their composition was as follows: total fats, 46.4 per cent; free fatty acids, 25.5 per cent; neutral fat, 17.4 per cent; soaps, 3.4 per cent, and total nitrogen, 3.3 Gm. Analysis of the gastric content disclosed no free hydrochloric acid, either during fasting or after stimulation with histamine. The test for dextrose tolerance showed a flat curve, the maximum rise in the sugar content of the blood being 12 mg. per hundred cubic centimeters.

Prompt and sustained improvement resulted from adequate liver therapy.

Case 8.—K. C. G., a girl aged 14, who had lived in North Carolina all her life, had suffered from chronic diarrhea for the past six years. The stools were greasy and bulky. Examination of the blood showed slight hypochromic anemia; there were 4,300,000 red cells and 82 per cent hemoglobin. Analysis

of the stools gave the following results: total fat, 52.7 per cent; free fatty acids, 23.8 per cent; neutral fats, 12.9 per cent; soaps, 16 per cent; total nitrogen, 4.3 Gm. Analysis of the gastric content showed 30 degrees free hydrochloric acid during fasting and 21 degrees after stimulation with histamine. The tests for dextrose tolerance showed a flat curve, the maximum rise in the sugar content of the blood being 13 mg. per hundred cubic centimeters.

At the time of writing the patient was receiving treatment with liver extract. Marked improvement was evident.

CASE 9.—B. C., a married man aged 30, who had lived on a farm in North Carolina all his life complained of diarrhea, weakness and loss of weight which began two and one half years before he was seen. Examination of the blood showed macrocytic hyperchromic anemia. Analysis of the stools gave the following results: total fat, 43.1 per cent; free fatty acid, 11.2 per cent; neutral fat, 8.1 per cent; soap, 23.8 per cent; total nitrogen, 12.9 Gm. Analysis of the gastric content showed no free hydrochloric acid during fasting and 37 degrees free hydrochloric acid after stimulation with histamine. The test for dextrose tolerance showed a flat curve, the maximum rise in the sugar content of the blood being 23 mg. per hundred cubic centimeters.

At the time of writing the patient shows marked improvement as the result of liver therapy.

Summary.—In the nine instances of the sprue syndrome reported here, the patients' age varied from 27 months to 60 years. Eight of nine patients showed macrocytic hyperchromic anemia; eight showed marked steatorrhea (the stools of A. B. [case 1] were not chemically analyzed); eight of nine patients had free hydrochloric acid in the gastric secretions after stimulation with histamine; all nine showed very low curves for the sugar content of the blood after the ingestion of 1.5 Gm. of dextrose per kilogram of body weight. The therapeutic response to liver extracts was prompt and marked in the nine patients.

The fundamentally identical findings in the nine cases which we have carefully studied, together with a review of the literature, have led us to agree fully with Thaysen[6] that celiac disease and sprue represent the childhood and the adult phase of the same underlying disease. The clinical picture of infantile sprue, with or without rickets, seems at first to have little in common with the picture of sprue in the adult. Infantile sprue and adult sprue, however, bear the same relationship to each other as do cretinism and myxedema. We shall consider now in more detail the separate elements of the sprue syndrome.

ETIOLOGY

There are certain features of celiac disease and sprue which point definitely to a deficiency state, however produced, as at least a factor in the production of the syndrome. The occurrence of osteoporosis and tetany in the child and of osteomalacia and tetany in the adult, associated in both with a low calcium and phosphorus content of the blood,

macrocytic hyperchromic anemia, xerophthalmia and night blindness,[8] mental changes, aphthous stomatitis and enteritis—these are changes recognizably due to deficiencies of accessory food factors. The gastro-intestinal mucosa is a highly specialized organ, resistant to infection and possessing great powers of regeneration. We believe that a deficiency of one or more accessory food factors lowers these powers of resistance and regeneration, leading to severe alterations of the functions of the gastro-intestinal mucosa. Eventually the uncorrected deficiency leads to a state of atrophy and dysfunction of the whole intestine. It is highly probable that, as in other deficiency states, cells of the whole body suffer. On the other hand, the condition is functional and amenable to treatment.

AGE AND MODE OF ONSET

Samuel Gee,[4] of St. Bartholomew's Hospital, published in 1888 a brief article entitled "On the Coeliac Affection," which deserves to be included among the minor medical classics. Phrased in a quaint, staccato style and written with the utmost brevity, his description has been but slightly amplified by subsequent observers. We quote from the opening paragraph: "There is a kind of chronic indigestion which is met with in persons of all ages, yet is especially apt to affect children between one and five years old." In support of Gee's assertion that the celiac disease "is met with in persons of all ages," we quote from Bailey Ashford's [9] article on sprue:

> In a smaller number of cases . . . sprue starts as a dystentery or as a more or less violent gastro-entero-colitis, with vomiting, fever, tenesmus and small mucous, often bloody stools. This mode of beginning is especially frequent among young children from two to five years of age.

Ashford found eighty-seven patients under 10 years of age among seven hundred and twenty patients with sprue in Puerto Rico. Miller [10] gave an excellent description of sprue occurring in a boy of 11, and Bennett, Hunter and Vaughan [11] have reported the occurrence of the sprue syndrome in patients aged 3½, 10, 11, 13 and 52 years. Weiss and his co-workers [12] among eighty-five patients with "tropical sprue" found five who were under 5 years of age.

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8. Riddell, W. J. B.: Coeliac Disease Associated with Night Blindness and Xerosis Conjunctivae, Tr. Ophth. Soc. U. Kingdom **53**:295, 1933.

9. Ashford, Bailey, in Christian, Henry A., and Mackenzie, J.: Oxford Medicine, New York, Oxford University Press, 1921, vol. 5, chap. 27, p. 640.

10. Miller, R.: Sprue Commencing at the Age of Eleven and One-Half Years, Tr. Roy. Soc. Trop. Med. & Hyg. **27**:413, 1934.

11. Bennett, T. I.; Hunter, D., and Vaughan, J. M.: Idiopathic Steatorrhoea (Gee's Disease), Quart. J. Med. **1**:603, 1932.

12. Weiss, C.; Landrón, F.; Costa-Mandry, O., and Weiss, D. W.: Summary of Investigations on the Etiology of Tropical Sprue in Porto Rico, Ann. Int. Med. **2**:1198 (May) 1929.

The onset of infantile sprue, or celiac disease, occurs most often between 1 and 2 years of age. Symptoms frequently had been present for several months before the parents sought medical advice, so insidious is the malady. In the early stages the patient loses his appetite, begins to lose weight, becomes cross and irritable and suffers from periods of moderate fatty diarrhea associated with vomiting. The progressive loss of weight, the weakness and the diarrhea finally bring him under medical observation.

Adult sprue and so-called nontropical sprue present similar symptoms, though the patient, being older, becomes aware earlier in the disease of subjective symptoms, which the infant cannot voice except by petulance and irritability. There is a sense of fulness after eating, due to gas in both the stomach and the intestine, accompanied by recurring diarrhea varying greatly in severity and later by soreness of the tongue and stomatitis. Diarrhea is not a constant feature; the patient may pass but one large fatty, ill smelling stool daily. The tendency is for the progress to be gradual, and the disease may be of very mild degree, showing exacerbations and remissions for years. Great loss of weight, nervousness, malaise and extreme fatty diarrhea are characteristics of the fully developed picture. A patient may lose as much as 50 per cent of his body weight, and rapid increase of weight often occurs as a result of proper treatment both in patients with celiac disease and in those with sprue.

PATHOLOGY

Neither sprue nor celiac disease presents a definite and constant pathologic picture. Hess and Saphir [13] have demonstrated by special staining methods a fibrosis of the pancreas with small cell infiltration, but there is no evidence that pancreatic deficiency exists in sprue. The changes in the intestines are those of chronic inflammation and edema, possibly the result of secondary infection, and atrophy of the whole intestine. The other organs show simply the effects of chronic malnutrition. The great depletion of the panniculous adiposus, common to both syndromes, is the most striking pathologic change. The absence of pathologic changes at autopsy strongly supports the theory that a disorder of metabolism, or a deficiency state, is a probable etiologic factor, and the studies of Miller and Rhoads [14] on the production of a chronic deficiency state in swine corroborate this opinion.

13. Hess, J. H., and Saphir, O.: Celiac Disease (Chronic Intestinal Indigestion), J. Pediat. **6**:1, 1935.

14. Miller, D. K., and Rhoads, C. P.: The Experimental Production of Loss of Hematopoietic Elements of the Gastric Secretion and of the Liver in Swine with Achlorhydria and Anemia, J. Clin. Investigation **14**:153, 1935.

STOOLS

We quote again from Gee:

> Signs of the disease are yielded by the faeces; being loose, not formed, but not watery; more bulky than the food taken would seem to account for; pale in color, as if devoid of bile; yeasty, frothy, an appearance probably due to fermentation; stinking, stench often very great, the food having undergone putrefaction rather than concoction.

This is an excellent description of the stools in cases of advanced sprue, though in the beginning the diarrhea is watery, and, indeed, in the mild form diarrhea may not be present.

The stools both of patients with sprue and of those with celiac disease contain an excess of fat, the fat content being about three times greater than normal, but it is generally agreed that the fat-splitting function is normal, in contrast to the condition existing in steatorrhea due to pancreatic deficiency. It has been shown [15] that the feces contain more fat than is present in the diet, thus indicating an excess excretion of fat through the intestinal epithelium. The low values for the calcium content of the blood frequently encountered in sprue and celiac disease are probably due to vitamin D deficiency and inadequate acidity of the intestinal contents, leading to poor absorption of calcium.[16] The values for calcium and phosphorus in the blood are frequently low both in sprue and in celiac disease. The percentage of nitrogen in the feces does not, as a rule, vary significantly from the normal. The stools are pale, thin and often frothy and "fermented" in appearance, and their bulkiness is out of all proportion to the intake of food. Remissions and exacerbations of the diarrhea are common, and costiveness may alternate with frequency.

Eight of the nine patients with the sprue syndrome observed by us had free hydrochloric acid in the gastric juice after stimulation with histamine; this is the almost universal rule, both in children [17] and in adults, the observations contrasting sharply in this respect with those on patients with pernicious anemia.

BLOOD

The anemia of sprue is typically first hypochromic and later becomes hyperchromic and macrocytic. There are, however, exceptions to this rule. The typical anemia of celiac disease, or infantile sprue, is hypochromic and only rarely becomes hyperchromic and macrocytic. This difference in the behavior of the bone marrow in the two syndromes

15. Bauer, E. L.: Celiac Disease, Am. J. Dis. Child. **35**:414 (March) 1928.

16. Macrae, O., and Morris, N.: Metabolism Studies in Coeliac Disease, Arch. Dis. Childhood **6**:75, 1931.

17. Ogilvie, J. W.: Gastric Secretion in Coeliac Disease, Arch. Dis. Childhood **10**:93, 1935.

has been urged by Parsons [18] as an argument for the separation of the two conditions. The point becomes less impressive when closely examined. The bone marrow of children reacts rarely in a hyperchromic, macrocytic fashion. So true is this that the very existence of pernicious anemia in childhood is a question of doubt. In the celiac syndrome, then, one can say only that the normal hypochromic reaction to injuries of the bone marrow in childhood obtains and that the underlying causes of the disease rarely [11] produce a reversal of this normal reaction. The condition is quite different in adults. In them the bone marrow frequently shows a hyperchromic, macrocytic reaction to diverse injuries (deficiency states, cancer, injuries to the liver, infestation with Dibothriocephalus latus, pregnancy, etc.). That it so reacts in patients with sprue, which is due in part, at least, to a deficiency state, is not surprising and certainly offers no defensible criterion for the separation of the syndromes of sprue and celiac disease. When improvement occurs, the blood picture of sprue loses its hyperchromic, macrocytic character and becomes hypochromic or normal.

BLOOD SUGAR CURVES

Low curves for sugar content of the blood (after the ingestion of 1.5 Gm. of dextrose per kilogram of body weight) have been found with greater than normal frequency in cases of "tropical" sprue, of "nontropical" sprue and of celiac disease. Thaysen [6a] regarded a rise of less than 40 mg. per hundred cubic centimeters as a low curve and stated that it has been found in only 5 per cent of normal persons. He observed persistently low curves in four of eight cases of "nontropical" sprue, in one of two cases of "tropical" sprue and in the one case of celiac disease which he studied. While the curves tend to be low, the rise is also prolonged over a period of two hours or more. Svensgaard [19] observed similar curves in two cases of celiac disease. She also observed marked rises in the sugar content of the blood when epinephrine was given in addition to 1.5 mg. of dextrose per kilogram of body weight. McLean and Sullivan [20] showed that the curve was low in fourteen children with celiac disease and that no tendency of the curve to rise after the ingestion of 1.75 Gm. of dextrose per kilogram of body weight was observed.

We believe that this constant low blood sugar curve is one of the most helpful differential findings in the sprue syndrome. In all our cases the curve was very low after the ingestion of 1.5 Gm. of dextrose

18. Parsons, L. G.: Celiac Disease, Am. J. Dis. Child. **43**:1293 (May, pt. 2) 1932.

19. Svensgaard, E.: Blood Sugar in Intestinal Infantilism, Acta pædiat. **9**: 22, 1929.

20. McLean, A. B., and Sullivan, R. C.: Carbohydrate Tolerance in Infants and Young Children with Celiac Disease, Am. J. Dis. Child. **38**:16 (July) 1929.

per kilogram of body weight (fig. 3). On the other hand, the intravenous injection of dextrose results in a prompt increase in the sugar content of the blood, though the curve rises to slightly lower levels than normal. The curve tends to return to normal levels as the patient recovers. Of eight cases of pancreatic steatorrhea Thaysen [6a] found that in seven there was a diabetic type of curve and in one a normal curve.

CENTRAL NERVOUS SYSTEM

The mournful, querulous, pessimistic facies of a patient with celiac disease mirrors the child's mental state. Such a child is "difficult"; nothing pleases him, and he is exceedingly irritable and emotional. Sleep is broken and disturbed, the child frequently crying out and moving restlessly.

The sufferer from adult sprue exhibits the counterpart of the nervous symptoms seen in the child. Such a patient is often emotionally unstable and depressed—exhibiting a strong leaning to pessimism—irritable, forgetful and filled with vague aches and pains. He is headstrong and even when reduced to skin and bones insists on dragging himself about (Ashford). Insomnia is troublesome. Subacute combined degeneration of the spinal cord is said not to occur in sprue, but this is incorrect, as it unquestionably does occur occasionally.[21] Paresthesia of the hands and feet is a common complaint.

RICKETS AND OSTEOPOROSIS

The changes in the bones in chronic steatorrhea due to various causes are most interesting. The principal change in sprue-celiac disease is osteoporosis. In infantile sprue, owing to the earlier age incidence, rickets is occasionally found. These changes in the bones are a result of the excessive excretion of calcium in the stools in the form of calcium soaps as well as of lack of absorption of vitamin D and of calcium.

McCrudden and Fales [22] first noted osteoporosis in celiac disease, associated with a negative calcium balance and an inadequate retention of phosphorus. Since then osteoporosis has often been observed and is the rule when the involvement is severe. Parsons in 1913 first demonstrated a case of celiac disease associated with definite rickets. There has been much controversy as to the type of rickets. Hess [23] stated:

> From the standpoint of rickets, the lesions in the bones which accompany celiac disease must be regarded as being the result of a deficiency in calcium.

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21. Weir, J. F., and Adams, M.: Idiopathic Steatorrhea (Nontropical Sprue): Metabolic Studies During Treatment; Report of a Case, Proc. Staff Meet. Mayo Clin. **9**:743, 1934.

22. McCrudden, F. H., and Fales, F. L.: Complete Balance Studies of Nitrogen, Sulphur, Phosphorus, Calcium and Magnesium in Intestinal Infantilism, J. Exper. Med. **15**:450, 1912.

23. Hess, A.: Rickets, Osteomalacia and Tetany, Philadelphia, Lea & Febiger, 1929.

On the other hand, Parsons considered the osteoporotic bones of patients with celiac disease to be potentially rachitic and he at times found low values for phosphorus. Fanconi found the values for phosphorus to be low in fifteen cases of "celiac rickets." The changes in the bone are considered by Parsons to pass through three distinct phases: (1) the usual type of infantile rickets (low values for phosphorus), (2) healing with arrested growth and subsequent osteoporosis and (3) late development of rickets associated with low values for calcium and sometimes for phosphorus in the blood. Late development of rickets occurs only if the disease is severe and of long standing. Parsons' youngest patient with "celiac rickets" was 5 years of age.

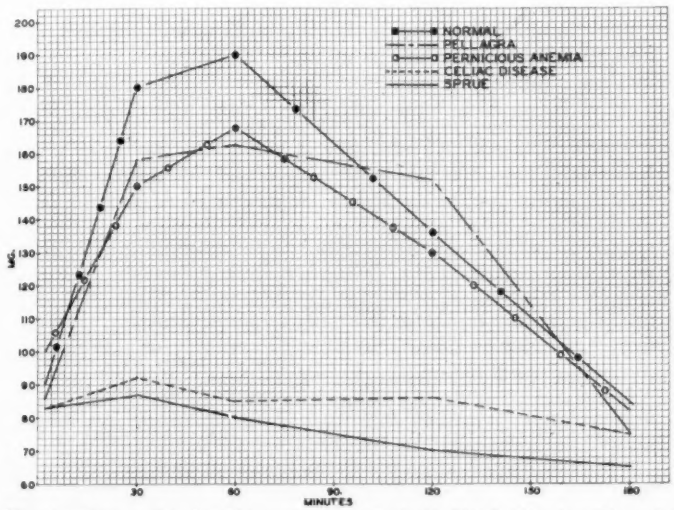

Fig. 3.—Curves showing the sugar content of the blood after ingestion of 1.5 Gm. of dextrose per kilogram of body weight.

Bennett, Hunter and Vaughan [11] found varying degrees of osteoporosis in twelve of fifteen patients with "idiopathic steatorrhea." Holmes and Starr [24] and Engel [25] each reported a case of "tropical" sprue with osteoporosis, but otherwise its presence or absence has seldom been mentioned. In the second and fourth cases of our series there was marked osteoporosis. Thaysen, in reviewing the literature on "non-

24. Holmes, W. H., and Starr, P.: A Nutritional Disturbance in Adults Resembling Celiac Disease and Sprue, J. A. M. A. **92**:975 (March 23) 1929.

25. Engel, A.: A Case of So-Called Sprue, Acta med. Scandinav. **75**:341, 1931.

tropical" sprue, found that seven of thirty-four patients had osteoporosis. Five of the seven also had active tetany. In tropical regions sprue seldom causes a marked lowering of the calcium content of the blood. This may be explained by the abundance of ultraviolet rays and their power to synthesize vitamin D from the inactive ergosterol of the skin. Fairley [26] in three cases of "tropical" sprue, however, found calcium concentration of less than 6.4 mg. per hundred cubic centimeters of blood. The inorganic phosphorus content of the blood in "nontropical" sprue was found by Scherer [27] in one case to be 2.41 and 2.27 mg. per hundred cubic centimeters, while Meyer's [28] patient had 2.02 mg. Both of these patients had tetany. In cases of celiac disease low values for phosphorus and calcium have often been found, and tetany is common.

Whether one accepts celiac disease as the infantile analog of sprue in adults is not a matter of indifference. Nothing is more certain than that the treatment of sprue with liver, first used by Bloomfield and Wycoff in 1926 has completely altered the outlook in cases of this disease. Rhoads and Miller [29] have shown that even the most severe and resistant sprue yields promptly to what Minot called "adequate liver therapy," and our experience confirms this in the most positive fashion. We believe that equally favorable results will follow the application of adequate liver therapy to celiac disease.

SUMMARY

From a detailed study of nine instances of the sprue syndrome the conclusion is reached that tropical sprue, nontropical sprue and celiac disease are identical in their etiology. An analysis of the separate components of the sprue syndrome reveals a clinical picture which is characteristic, permitting ready and accurate differential diagnosis. Prompt improvement follows administration of liver in adequate amounts.

NOTE.—Since this paper was submitted for publication we have studied five additional instances of sprue. One patient of 17 showed typical dwarfism as described in this paper; the other four were adults. The study of these patients has served to confirm the conclusions which we have stated.

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26. Fairley, N. H.: Sprue: Its Applied Pathology, Biochemistry and Treatment, Tr. Roy. Soc. Trop. Med. & Hyg. **24**:131, 1930.

27. Scherer, E.: Ein Fall von einheimischer Sprue, Klin. Wchnschr. **8**:1625 (Aug. 27) 1929.

28. Meyer, A.: Ueber Coeliakie, Ztschr. f. klin. Med. **119**:667, 1932.

29. Rhoads, C. P., and Miller, D. K.: Intensive Liver Extract Therapy of Sprue, J. A. M. A. **103**:387 (Aug. 11) 1934.

EXTENSIVE ARTERIAL AND VENOUS THROMBOSIS COMPLICATING CHRONIC ULCERATIVE COLITIS

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It is generally agreed that chronic ulcerative colitis is one of the most serious of the diseases that afflict the digestive tract of man. Its complications may be equally serious. Fortunately, they are rare, but, unfortunately, when they do occur in a given case they are likely to be multiple.[1]

One of the very serious complications of chronic ulcerative colitis is extensive thrombosis of the blood vessels. Among fifteen hundred cases of chronic ulcerative colitis which we have observed thrombophlebitis or arterial thrombosis which was extensive enough to become a grave clinical problem occurred in eighteen. Less serious subclinical thrombosis of small vessels, chiefly the veins, has occurred more frequently than extensive thrombosis. In patients who come to necropsy, emboli and thrombi have been found in various places, such as the pelvic plexuses, lungs, spleen and kidneys. Among the last forty-three of our patients who died of chronic ulcerative colitis, emboli and thrombi were found in fourteen.

The six cases reported here have been under our observation in the last two years, whereas nine other cases have been observed in the eight prior years. This suggests an increased incidence of this complication and made this report seem timely. Because some of these patients received the anticolitis serum, some observers might suggest that the thrombosis occurred as a result of its administration; however, in one case, in which the thrombosis was severe, the patient did not receive any serum, and this phenomenon has occurred in many other cases in which serum was not employed.

REPORT OF CASES

CASE 1.—A man, aged 26 years, came to the Mayo Clinic on Dec. 2, 1933, because of severe chronic ulcerative colitis, which had been present for a year. The condition had been progressive. His normal weight was 135 pounds (61.2 Kg.). He was a husky, athletic person, a university graduate and a teacher. Since his

From the Division of Medicine, the Mayo Clinic.

1. Bargen, J. A.: The Management of Colitis, edited by Morris Fishbein, Garden City, N. Y., Doubleday, Doran & Company, Inc., 1935.

condition had been progressive, a cecostomy was performed elsewhere on July 28, 1933. However, this was not followed by the desired improvement, so that when he arrived at the clinic he was having between fifteen and twenty-five stools and rectal discharges daily, containing much pus and quantities of blood, both liquid and clotted. His weight was 104 pounds (47.2 Kg.). There was moderate secondary anemia. The value for the hemoglobin was 7.5 Gm. per hundred cubic centimeters of blood. There were 3,310,000 erythrocytes and 9,200 leukocytes per cubic millimeter of blood. Of the total number of leukocytes, 34 per cent were nonfilamented polymorphonuclear neutrophils and 22 per cent were filamented polymorphonuclear neutrophils. Many stools were examined, and no parasites, ova, acid-fast bacilli or unusual bacteria were found. The proctoscopic examination revealed the usual picture of an ulcerated, granular mucous membrane which bled easily. The activity was 3, on a basis of 4, and the lumen was limited in some places to 1.5 cm. Roentgenologic examination of the colon revealed extensive and advanced disease of the entire colon.

The specific antibody solution was administered intramuscularly; the opening produced by the cecostomy was allowed to close, and two blood transfusions (one on December 6 and one on December 11) were given. Improvement was slow but progressive, and by Jan. 1, 1934, the administration of the autogenous vaccine was begun. The patient was dismissed on February 1. At that time he was greatly improved clinically and weighed 155 pounds (70.3 Kg.), although he was still averaging about ten stools daily, which did not contain any blood. Two weeks before his dismissal, the value for the hemoglobin was 9.2 Gm. per hundred cubic centimeters of blood, and there were 4,320,000 erythrocytes and 5,500 leukocytes per cubic millimeter of blood.

He continued to improve until three weeks after returning home, at which time pain developed in the left popliteal space. One week later he noted numbness and coldness in the left foot and cyanosis of the toes. Two weeks later he returned to the hospital in Rochester. At that time examination revealed that the left foot was definitely colder than the right, abnormally pale when elevated and abnormally red when dependent. There was some diminution of sensation and muscle power of the left leg and absence of pulsation in the left femoral, popliteal, posterior tibial and dorsalis pedis arteries. The pulsations were normal in the right leg. A diagnosis of progressive thrombosis of the left popliteal and femoral arteries, with secondary ischemic neuritis was made. Several blood cultures on successive days at that time did not reveal any organisms. The temperature, which rarely had gone above 100 F. during his previous stay in the hospital, averaged 102 F. Ten days after his admission the patient complained of the right foot "going to sleep," and within twelve hours this foot was found to be white and cold, with collapsed veins. There were normal pulsations in the right femoral artery, but the pulsations in the right popliteal artery were diminished. There was no pulsation in the dorsalis pedis and posterior tibial arteries. Three days later pulsations had disappeared in the popliteal and femoral arteries, and the leg was co'd and cyanotic to 6 inches (15 cm.) above the knee. There were severe pain and inability to move the foot and toes. The plasma coagulability index (Nygaard [2]) was normal (1.1), and the number of blood platelets was also normal, 370,000 per cubic millimeter. On the next day the left leg and foot became more painful and cyanotic than they had been. At the end of another week there was dry gangrene of the sole of the right foot. Two weeks later there was well delimited

2. Nygaard, K. K.: Coagulability of the Blood Plasma, Proc. Staff Meet., Mayo Clin. **7**:544 (Sept. 21) 1932.

dry gangrene of both legs and feet, which extended above the knees (fig. 1). Because of pain and increasing toxemia, amputation of the legs seemed unavoidable and was undertaken on April 16. For two days the patient seemed to rally, but after that failure was progressive, and he died on April *22*, six weeks after the onset of the arterial occlusion.

Examination of the amputated legs showed that all the large arteries and veins of the legs were completely occluded by gray-red thrombi. Histologic examination of the lower part of the femoral arteries, the popliteal arteries and the upper part of the posterior tibial arteries showed that the thrombi consisted of degenerated fibrin and erythrocytes; they contained practically no cell nuclei, and there was no evidence of organization. The arterial walls appeared normal and did not disclose any reaction. The thrombus in the left popliteal vein was partly organized at the margin and in a band across the center. The media and adventitia of the vein showed moderate infiltration with histiocytes and fibroblasts. The right

Fig. 1.—Extensive dry gangrene of the legs, a result of arterial thrombosis.

popliteal vein was filled with disintegrating débris and polymorphonuclear leukocytes, and there was marked irregular infiltration of the wall of the vein with polymorphonuclear leukocytes. The picture was that of simple thrombosis of the arteries and of suppurative thrombosis of the right popliteal vein, which probably was secondary to the more distal gangrenous process. There was no pathologic evidence of thrombo-angiitis obliterans, and there was no evidence of arteriosclerosis.

At necropsy there was found to be complete thrombosis of both iliac and both femoral arteries and of the abdominal aorta, which extended above the origin of the renal arteries, which also were completely thrombosed (fig. *2*). There was partial infarction of the right kidney and complete infarction of the left kidney. There also was thrombosis of both iliac and both femoral veins, the inferior vena cava and the left renal vein. Arteries in the lower lobes of both lungs were found to be occluded by partially organized thrombi (probably emboli originally). Histologic examination of the aorta and of the iliac arteries revealed a degenerated, homogeneous acellular thrombus, but there was no organization. There were slight

infiltration of the arterial walls with lymphocytes and fibroblasts and moderate dilatation and congestion of the vasa vasorum. In the iliac veins the picture was the same, except that the thrombi were definitely organized at their margins and there were a few small collections of polymorphonuclear leukocytes in the region of the intima. On the basis of the histologic findings, the oldest thrombosis was probably in the left popliteal and femoral veins, although this had not been apparent clinically (fig. 3).

This is the only case on record in which there was progressive arterial thrombosis in connection with advanced chronic ulcerative

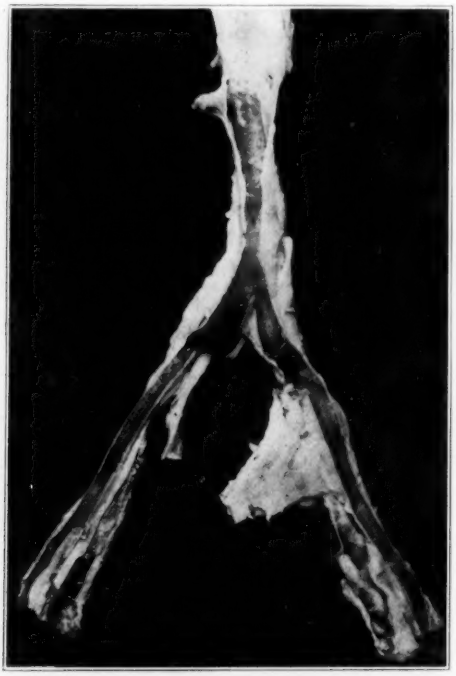

Fig. 2.—Extensive thrombosis of the aorta and the iliac arteries.

colitis. Observation of the clinical picture in such a case is most distressing. We are frankly pleased that this complication is such a rare one.

Case 2.—A single woman, aged 21, came to the clinic on Nov. 25, 1934, on account of severe chronic ulcerative colitis which had been present for five months. The condition had become progressively worse from the time of its onset. The patient had lost 30 pounds (13.6 Kg.) in weight. She was averaging about one dozen rectal discharges every twenty-four hours. The stools consisted chiefly of large quantities of fresh and clotted blood and pus. A proctoscopic examination revealed the typical picture of chronic ulcerative colitis, with marked activity.

She was too ill at that time to warrant roentgenologic examination. The temperature was 102 F. at the time of her admission. The value for the hemoglobin was 7 Gm. per hundred cubic centimeters of blood. There were 3,830,000 erythrocytes and 12,200 leukocytes per cubic millimeter of blood. Of the leukocytes, 71 per cent were polymorphonuclear neutrophils, divided on the basis of all leukocytes present as follows: 48 per cent nonfilamented and 23 per cent filamented. Treatment with the specific antibody solution (concentrated serum) was begun at once, and during the first week it was necessary to administer dextrose solution intravenously because the patient was unable to take anything by mouth. A transfusion of 250 cc. of blood was also given. Improvement was slow but progressive;

Fig. 3.—Photomicrograph of a histologic section of the left external iliac artery, showing almost complete absence of organization of the thrombus and of inflammatory reaction in the arterial wall. Hematoxylin and eosin stain; × 85.

by the end of the month the bleeding had stopped and the value for the hemoglobin had increased to 9.3 Gm. per hundred cubic centimeters of blood. At that time there were 4,410,000 erythrocytes per cubic millimeter of blood but there were still 12,400 leukocytes per cubic millimeter. Sixty-one per cent of the leukocytes were nonfilamented polymorphonuclear neutrophils, and 13 per cent were filamented polymorphonuclear neutrophils. For several weeks the condition seemed stationary and the rectal discharges numbered five in twenty-four hours at a maximum. On December 29, thirty-five days after her admission to the hospital, signs of thrombophlebitis developed in the lower part of the right leg.

There were pain and some swelling. Four days later both legs became markedly swollen and painful and there was definite pitting edema. The superficial veins were prominent and distended, and there were dilated superficial veins over the right lower quadrant of the abdomen. The temperature, which had previously been elevated to 101 F. in the afternoon, fell to 97 F. The pulse rate rose to 130. The legs were elevated, and hot packs were applied. The edema of the legs disappeared partly but not completely. Pain became less marked than it had been, but the patient became progressively weaker and her condition was more toxic than before. It is of note that the plasma coagulability index

Fig. 4.—Extensive advanced and destructive chronic ulcerative colitis.

(Nygaard) was definitely elevated (1.4) forty-eight hours after the onset of the thrombophlebitis; the number of blood platelets was 600,000 per cubic millimeter at that time. Seven days later the plasma coagulability index was the same as it was at that time and the blood platelets numbered 262,500 per cubic millimeter of blood. Three days before death the plasma coagulability index was 1.8 and there were 130,000 blood platelets per cubic millimeter. The value for the hemoglobin had dropped to 5.6 Gm. per hundred cubic centimeters of blood, and the number of erythrocytes had decreased to 3,190,000 per cubic millimeter. When death occurred, on Jan. 18, 1935, the chronic ulcerative colitis was found to be massive and extremely destructive and to involve the entire colon and terminal portion of the ileum (fig. 4). A gray-white thrombus, which was firm and adher-

ent, filled the lower portion of the inferior vena cava. The thrombus extended from the level of the left renal vein (fig. 5), into which it projected, to the bifurcation of the inferior vena cava and thence into the common iliac veins, into the external iliac vein and into the hypogastric veins, filling all these veins.

Gray thrombi (emboli) were found also in the arteries to the upper lobe of the right lung and to the lower lobe of the left lung.

Histologic examination of the vena cava and iliac veins revealed that the majority of the thrombi consisted of degenerated blood and fibrin, with few cell nuclei. The margins of the thrombi were made up of erythrocytes and a few

Fig. 5.—Extensive thrombosis of the inferior vena cava and of the common iliac veins.

fibroblasts and were adherent to the walls of the veins. Small collections of lymphocytes and a few fibroblasts were scattered through the walls of the veins, chiefly in the inner circular layer of the muscle. The vasa vasorum appeared normal. The picture suggested primary thrombosis with slight secondary reaction in the wall of the vein. The thrombi in the pulmonary arteries were attached to the arterial wall only at one small area and showed definite organization at that point, which suggested that they were emboli that were several days old.

Case 3.—A married woman, aged 31, was brought to the hospital in an ambulance on April 23, 1934. She had had diarrhea for twenty-nine years, or since the age of 2 years. This followed a severe attack of scarlet fever. She could not

recall having had less than from six to eight bowel movements in twenty-four hours. The stools were watery and contained various quantities of blood. Occasionally there were severe exacerbations, during which she had many purulent bloody rectal discharges every twenty-four hours. In spite of this, she enjoyed rather good health, attended school, played and grew, and her weight was about the average for a child of her age. She consulted numerous physicians and had various treatments. Her maximal weight was 127 pounds (57.6 Kg.). In October 1933 she commenced to lose strength and weight, became very pale and had attacks of abdominal bloating and severe cramplike pain. The pain was situated in the left half of the abdomen and often was colicky. After that, there was more blood in the stools than there had been before. In December 1933, edema of the ankles and the legs appeared and extended to the knees. There also was a slight edema of the hands and some dyspnea. The physician whom she consulted in January 1934 ordered her to bed at once and advised a high caloric diet, which she then followed. When her condition warranted it, he made a proctoscopic examination and was the first to make a diagnosis of chronic ulcerative colitis. She was very ill; there were periods of continuous vomiting, and then there was some improvement. However, during the two weeks before she came to the clinic, she again became worse than she had been. At that time there were some vomiting and signs of obstruction. At the time of her admission to the hospital, which was at 6:30 p. m., her weight was 104 pounds (47.2 Kg.), she appeared very pale, the pulse was rapid, the abdomen was distended slightly and there was tenderness in the left lower quadrant. At 8:30 p. m., she was suddenly seized with excruciating pain in the left lower quadrant of the abdomen. That portion of the abdomen became exquisitely tender. Symptoms of shock developed; the pulse became rapid and thready, and the temperature was 101 F. A diagnosis of chronic ulcerative colitis with perforation of the sigmoid flexure was made. Because of the history of obstruction and the marked change in symptoms, a superimposed neoplasm was suspected.

The foot of the bed was elevated, sedatives were administered, nothing was allowed by mouth and complete rest was instituted. Twelve hours later a huge mass appeared in the left lower quadrant of the abdomen. The aforementioned symptomatic measures were continued, and the fluid balance of the body was maintained by the intravenous administration of dextrose solution. The mass rapidly decreased in size, and the symptoms of perforation seemed to subside.

She had definite anemia; the value for the hemoglobin was 8.5 Gm. per hundred cubic centimeters of blood, and the erythrocytes numbered 4,480,000 per cubic millimeter. On the fifth day after her admission to the hospital pain and tenderness developed in the calf of the left leg. There was some swelling of the ankle also. Twenty-four hours later there were pain in the left thigh and groin, marked swelling of the entire leg and congestion and dilatation of the superficial veins (fig. 6). Tenderness in the calf of the right leg was also noted for a short period. There was no increase in temperature or pulse rate. Elevation of the limb and the application of hot packs improved the condition, but two days later there was another attack of severe generalized abdominal pain and a concomitant severe pain in the calf of the left leg. The foot became cold and very cyanotic.

Pulsations were present in the femoral artery but were not felt in the dorsalis pedis artery, although the huge swelling of the leg made the accuracy of palpation questionable. The patient died twenty-four hours later, seven days after her admission to the hospital. It is noteworthy that after each daily intravenous injection of a solution containing 10 per cent dextrose and 1 per cent sodium chloride, thrombosis developed at the site of injection.

Necropsy revealed a very advanced, destructive chronic ulcerative colitis of the entire colon. There was complete obliteration of any demarcation of the ileocecal junction. A polypoid carcinoma of the sigmoid flexure and a mucoid

Fig. 6.—Extensive thrombophlebitis of the left iliac vein, showing massive swelling of the entire leg and marked congestion of the skin (infra-red photograph).

carcinoma of the splenic flexure were also present (fig. 7). The entire left common iliac, the left hypogastric, the left external iliac and the left femoral vein were found to be occluded by gray-red friable thrombi. A small infarct was found in the lower lobe of the right lung.

Histologic examination of the iliac veins revealed that the thrombi consisted almost entirely of fibrin and erythrocytes (fig. 8). There was early fibroblastic organization at the margins only, and no inflammatory reaction was present in the walls of the veins.

Case 4.—A single woman, aged 24, was brought to the clinic in an ambulance on Dec. 24, 1933. She had symptoms of severe and very active chronic ulcerative colitis. The maximal number of rectal discharges in twenty-four hours, during the first week of her stay in the hospital, was eighteen. The temperature ranged between 101 and 102 F. daily. The rectal discharges consisted largely of bloody purulent material. The blood was red, fresh and clotted. A proctoscopic examination suggested the activity to be 2, on the basis of 4. It was not until January 18 that a roentgenologic examination of the colon seemed warranted; this revealed destructive chronic ulcerative colitis of the entire colon. The value for the hemo-

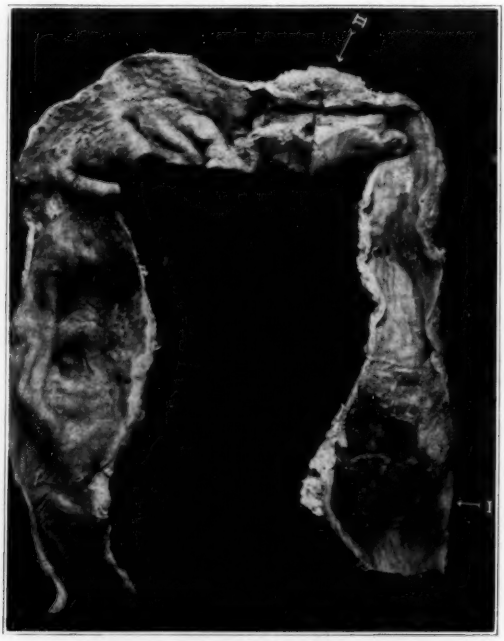

Fig. 7.—Markedly destructive chronic ulcerative colitis with (*I*) a polypoid carcinoma of the sigmoid flexure and (*II*) an annular scirrhous carcinoma of the transverse colon.

globin at the time of her admission was 6.6 Gm. per hundred cubic centimeters of blood. There were 3,360,000 erythrocytes and 25,200 leukocytes per cubic millimeter of blood. Of these, 70 per cent were nonfilamented polymorphonuclear neutrophils and 15 per cent were filamented polymorphonuclear neutrophils. The rate of sedimentation was markedly increased, being 160 mm. in a two hour period. Microscopic examination of the rectal discharges failed to reveal parasites or ova, but a pure culture of the diplostreptococcus grew in the cultures. Roentgenologic examination of the chest did not reveal any disease. Specific antibody

solution (concentrated serum) was administered intramuscularly, and two blood transfusions were given, one on the fourth and one on the tenth day of the patient's stay in the hospital. The fever gradually receded, so that by the eighteenth day in the hospital the temperature was normal. On the twenty-first day, severe pain in the right lower part of the abdomen occurred, with a subsequent rise in the temperature. During the next two weeks, there was fever; the lowest temperature was 102.5 F., and the maximal was 105 F. Two weeks after the onset of this attack pain occurred in the left lower quadrant of the abdomen. This pain had all the features of that caused by acute colonic perforation. Dextrose solution was

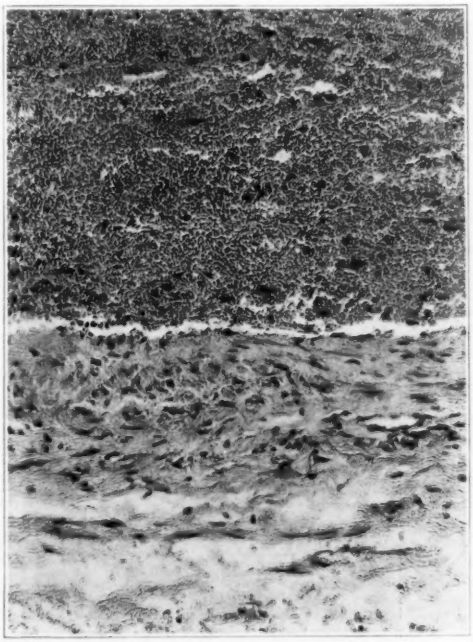

Fig. 8.—Photomicrograph of histologic section of left iliac vein, showing almost complete lack both of organization of the thrombus and of inflammatory reaction in the wall of the vein. Hematoxylin and eosin stain; × 125.

administered intravenously, no fluid was administered by mouth and a solution of gentian violet and serum was administered intravenously. On February 16, fifty-six days after her admission to the hospital, a swelling of the entire left leg and thigh developed (fig. 9). This abated after the leg had been elevated for a few days. On February 22, the right leg became markedly swollen and edematous, with areas of ecchymosis and dilatation of the superficial veins. Six days later, another sudden attack of severe pain developed in the right lower quadrant of the abdomen. The pain extended around to the back. She vomited and became very pale, but there was no rise in the temperature or the pulse rate.

After a long and stormy course the patient completely recovered. She had passed through a state of what was considered clinically to be massive bilateral thrombophlebitis of the iliac and femoral veins and possibly a subsequent intra-abdominal thrombophlebitis. She also had passed through a stage of subacute colonic perforation. She was dismissed on March 3, 1934. Subsequent reports indicated satisfactory progress, the latest of these being on May 28, 1936.

Fig. 9.—Thrombophlebitis of the left iliac vein, showing swelling of the entire leg and dilated prominent superficial veins, particularly of the thigh (infra-red photograph).

CASE 5.—A youth, aged 19 years, was brought to the hospital because of severe chronic ulcerative colitis, which had been present for eight months. While serving as a caddy on a golf course, he suddenly was seized with cramps and a desire to defecate. A stool which was passed at that time contained blood. His symptoms became progressively worse. At the time of his admission to the hospital, he was averaging twelve bloody, purulent rectal discharges daily. The

activity of the disease, from a protoscopic standpoint, was 2, on the basis of 4. Ten successive examinations of the stools, on as many days, failed to reveal any parasites or unusual bacteria except the diplostreptococcus of chronic ulcerative colitis. A roentgenologic examination of the colon was not made because of the severe, systemic reaction of the disease. There was daily fever during his stay in the hospital, and marked anemia. The lowest value for the hemoglobin was 4.86 Gm. per hundred cubic centimeters of blood. There were 2,350,000 erythrocytes per cubic millimeter of blood. The normal weight had been 118 pounds (53.5 Kg.). The weight at the time of admission was 85 pounds (38.6 Kg.). The specific antibody solution (concentrated serum) was administered, and one blood transfusion was given. The patient made slow but progressive improvement.

On the twenty-seventh day after his admission to the hospital, a massive swelling of the left leg developed. This responded to some extent to elevation of the limb and to the application of hot packs. The patient left the hospital five days later, to continue treatment at home. The clinical picture was that of thrombophlebitis of the left iliac vein, which complicated severe chronic ulcerative colitis.

Case 6.—A man, aged 22, came to the clinic on May 23, 1934, because of rather severe chronic ulcerative colitis, which had been present for five months. He had been having fifteen bowel movements daily for several months. There were loss of weight and general wasting and an increase in the temperature each afternoon. The amount of blood in the stools was not great. At the time of his admission to the hospital he was averaging between eight and nine stools daily, but he appeared more ill than this might suggest. Proctoscopic examination revealed the typical picture of chronic ulcerative colitis, and roentgenologic examination revealed involvement of the entire colon. Roentgenologic examination of the thorax did not reveal any disease. The value for the hemoglobin was 13.3 Gm. per hundred cubic centimeters of blood. There were 4,380,000 erythrocytes and 10,700 leukocytes per cubic millimeter of blood. Of the total number of leukocytes, 37 per cent were nonfilamented polymorphonuclear neutrophils and 20 per cent were filamented polymorphonuclear neutrophils. The sedimentation rate was greatly increased, reaching 118 mm. in two hours. The urine was essentially normal. On the sixth day of his stay in the hospital his temperature rose to 103 F. and the number of leukocytes increased to 16,600 per cubic millimeter. At that time cyanosis and marked swelling of the entire left leg appeared. There were pain and tenderness in the groin and distention of the cutaneous veins of the thigh and the lower part of the abdomen. A diagnosis of thrombophlebitis of the left femoral and iliac veins was made. Two weeks later thrombophlebitis appeared in the upper part of the long saphenous vein. This gradually descended to the knee. The vein was very tender, swollen and indurated, and the skin over it was red. Four days later thrombophlebitis developed in the right median basilic vein at the site of a venipuncture and spread up the vein for a distance of 10 cm. On the fourteenth day after the onset of the iliac thrombophlebitis, the coagulability index of the plasma was 1.3 and the blood platelets numbered 750,000 per cubic millimeter.

After a month of treatment by elevation of the limb, the application of hot moist packs to the leg and the application of roentgenotherapy to the long saphenous vein, the pain, local tenderness and almost all the swelling of the leg disappeared, and the patient was allowed to be out of bed.

The treatment of the colitis included the administration of the specific antibody solution (concentrated serum) as well as the usual diet and the administration of anticolitis vaccine. Complete relief from symptoms of colitis followed, and a report on May 1, 1935, revealed that the patient has remained well.

COMMENT

It is of interest that all these patients were young adults, between the ages of 19 and 31 years. At the time of the development of the thrombosis, the patients had been at rest in bed for several days or weeks and therefore were subjected to venous stasis in the lower extremities. All except one had rather marked secondary anemia. In all these cases large veins, such as the femoral and iliac veins and even the vena cava, were involved. All these patients had severe chronic ulcerative colitis, with fever and evidence of toxemia. Colonic perforation occurred in two of the six cases. The roentgenograms, in those cases in which roentgenologic examination was possible, revealed extensive intestinal disease. In our experience it is only in the cases of the most severe involvement in which there are very acute exacerbations of the disease that roentgenography seems inadvisable. The pathologic specimens which were obtained at necropsy illustrate further the immensely destructive colonic process in the cases in which death occurred. Local or even diffuse peritonitis, or at least peritoneal irritation, was also present in these cases.

The exact pathogenesis of venous thrombosis and thrombophlebitis is still debatable. Its occurrence as a complication of various severe infectious diseases [3] which are accompanied by generalized toxemia, particularly typhoid, pneumonia, and influenza, was reviewed by Welch [4] in 1898. It is also seen in association with anemia; some of the early cases that were described were associated with chlorosis, in which there was no evidence of infection. Rest in bed, with resultant venous stasis, is considered to be a factor in certain cases, particularly in those of postoperative thrombophlebitis (Robertson [5]). It is not surprising, therefore, that thrombosis of the veins of the legs should complicate chronic ulcerative colitis, in which all three factors—severe infection with toxemia, anemia and venous stasis—are present. As an inciting factor, there is the possibility of local damage to the large iliac veins, as the result of the neighboring peritonitis. Also, thrombi may form in small veins of the rectum close to ulcers and propagate through branches of the hypogastric to the common iliac veins. Arterial thrombosis has been described as a rare complication of typhoid, pneumonia and influenza, as well as of other infectious diseases. However, it has not been described as occurring in chronic ulcerative colitis, and such a

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4. Welch, W. H.: Thrombosis, in Allbutt, Clifford, and Rolleston, H. D.: A System of Medicine, New York, The Macmillan Company, 1909, vol. 6, p. 691.

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progressive and extensive simple arterial thrombosis, with venous thrombosis as well, as was seen in case 1, is a very unusual event, and is rarely seen in a young person whose arteries otherwise are normal.

The histopathologic picture and the location of the involvement chiefly in large venous trunks show that the thrombosis associated with chronic ulcerative colitis is out of all proportion to any changes which can be seen in the vessel walls. There may be some small focus of inflammation in a vessel which acts as a starting point, but the extensive propagation of the thrombus suggests that there is also an increased tendency of the blood itself to produce thrombosis. Such evidence of phlebitis or arteritis as is seen in the sections is minimal and can be interpreted as chiefly secondary to the presence of the thrombus. Attempts at organization of the thrombi are slow and rather feeble.

At the Mayo Clinic, in a series of cases of chronic ulcerative colitis, the incidence of massive thrombosis in the vessels of the legs was slightly more than 0.1 per cent. This complication must be regarded as of serious prognostic import. In three of the six cases which are reported the patient died. All the deaths were caused by toxemia and not by embolism. It seems probable that the thrombosis in such cases is caused by the combination of local infection, generalized toxemia, alterations in the blood and venous stasis.

THERAPEUTIC EFFECT OF TOTAL ABLATION OF NORMAL THYROID ON CONGESTIVE FAILURE AND ANGINA PECTORIS

XVIII. THE CARDIAC OUTPUT FOLLOWING TOTAL THYROIDECTOMY IN PATIENTS WITH AND WITHOUT CONGESTIVE HEART FAILURE, WITH A COMPARISON OF RESULTS OBTAINED WITH THE ACETYLENE AND ETHYL IODIDE METHODS

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Studies of the cardiac output in spontaneous myxedema are few. Various observers [1] have reported a decrease in the minute volume output of the heart in patients with hypothyroidism. The recently reported work of Blumgart and his associates [2] in establishing the value of total

This investigation was aided by a grant from the William W. Wellington Memorial Research Fund of Harvard University.

From the Medical Service and Medical Research Laboratories of the Beth Israel Hospital and the Department of Medicine, Harvard University Medical School.

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ablation of the thyroid gland in the treatment of chronic intractable cardiac disease made it advisable to study the cardiac output and related aspects of the circulation in hypothyroidism induced by this operation. Data obtained by the acetylene method [3] for seven patients with no evidence of congestive failure were reported in a previous publication.[4] This communication presents preoperative and postoperative studies of the cardiac output by means of the ethyl iodide method [5] in patients with and without congestive failure on whom total thyroidectomy was performed. Results obtained by this method and by the acetylene method in the same patients are compared.

MATERIAL AND METHODS

Observations have been made on twenty-three patients in whom hypothyroidism developed subsequent to total ablation of the thyroid gland. Eleven patients had no history or signs of congestive heart failure; these patients were operated on for the relief of angina pectoris (cases 1, 2, 3, 5, 6, 7, 8, 9, 10), for latent hyperthyroidism with angina pectoris (case 11) or for the control of severe diabetes (case 4). Of this group five subjects were men and six were women; the ages varied from 23 to 65 years. Another group, consisting of twelve patients (cases 12 to 23), were operated on for the relief of congestive failure. Of these, nine were men and three were women; the ages varied from 23 to 66 years. The preoperative measurements were made shortly before operation, when the patients were in the best possible condition, i. e., after they had had a period of rest in bed and had received full therapeutic doses of digitalis and in most instances intravenous injections of salyrgan as well. There was no perceptible edema of the extremities and at most very few râles over the bases of the lungs; slight or moderate enlargement of the liver was present in many patients at the time the measurements reported here were made. The hemoglobin content was 85 per cent or higher in all the patients studied. Many patients showed slight or moderate sclerosis of the peripheral arteries; the blood pressure in most of these instances was elevated.

In determining the cardiac output by the acetylene method the following procedure was used: All measurements were made with the patient in the postabsorptive state, under basal conditions, in the semirecumbent position, after a rest of from one-half to one hour. The basal metabolic rate was first measured in duplicate with a Collins-Benedict-Roth spirometer and calculated according to the Aub-DuBois normal standards. The arterial blood pressure was next measured with a mercury manometer with the standard cuff. The figures in the table represent the averages of several readings. The pulse rate was counted twice before each measurement of the cardiac output. Two measurements of the arteriovenous

3. Grollman, A.; Friedman, B.; Clark, G., and Harrison, T. R.: Studies in Congestive Heart Failure: XXIII. A Critical Study of Methods for Determining the Cardiac Output in Patients with Cardiac Disease, J. Clin. Investigation **12**: 751, 1933.

4. Altschule, M. D., and Volk, M. C.: The Minute Volume Output and the Work of the Heart in Hypothyroidism, J. Clin. Investigation **14**:385, 1935.

5. Starr, I., and Gamble, J. C.: An Improved Method for the Determination of Cardiac Output in Man by Means of Ethyl Iodide, Am. J. Physiol. **87**:450, 1928.

TABLE 1.—*Data on Patients without Congestive Failure*

Case	Age, Years	Basal Metabolic Rate, Deviation from Normal, Percentage	Oxygen Consumption, Cc. per Minute	Arteriovenous Oxygen Difference, Volumes per Cent	Cardiac Minute Volume Output, Liters	Cardiac Index	Pulse Rate	Cardiac Output per Beat, Cc.	Blood Velocity, Arm to Tongue Circulation Time, Seconds	Venous Pressure, Cm. Water	Arterial Pressure, Systolic, Mm. Mercury	Arterial Pressure, Diastolic, Mm. Mercury	Vital Capacity, Cc. per Sq. Meter	Work per Minute, Kilogrammeters	Work per Beat, Grammeters	Method*	Comment
1	65	—35	167	6.50	2.6	1.3	58	44	16	6.9	120	76	1,150	3.4	59	A	14 months after operation; thyroid 1/10 grain (0.006 Gm.) daily
		—31	178	6.15	2.9	1.4	64	45	21	5.0	130	76	1,250	4.1	63	EI	23 months after operation; thyroid 1/10 grain (0.006 Gm.) daily
2	58	—23	155	5.90	2.6	1.6	65	41	20	...	136	88	1,280	4.0	61	EI	22 months after operation; thyroid 3/10 grain (0.018 Gm.) three times a day
3	58	—28	138	6.70	2.1	1.3	65	32	..	7.4	186	110	940	4.1	64	A	11 months after operation; thyroid 1/10 grain (0.006 Gm.) daily
		—17	158	6.00	2.6	1.6	81	33	18	6.0	170	110	1,250	4.9	61	EI	16 months after operation; thyroid 1/10 grain (0.006 Gm.) twice a day
4	23	—10	179	5.80	3.1	2.0	71	42	10	...	114	60	2,000	3.5	48	A	3½ months after operation; thyroid 5 grains (0.324 Gm.) daily
		—20	161	5.80	2.8	1.8	55	50	15	±0	124	80	2,100	3.9	70	A	4 months after operation; no thyroid for 2 weeks
		—15	166	5.80	3.0	1.9	87	34	..	...	110	60	1,800	3.5	40	EI	15 months after operation; thyroid 1/10 grain (0.006 Gm.) daily
5	53	—34	154	6.95	2.2	1.2	56	40	31	...	110	90	1,330	3.0	54	A	4 months after operation
		—15	193	5.85	3.3	1.9	79	42	22	...	116	86	1,530	4.5	58	A	5 months after operation; thyroid 1 grain 3 times a day
		—29	165	6.35	2.6	1.4	76	34	37	3.1	104	76	1,380	3.2	42	A	9 months after operation; thyroid ¼ grain (0.016 Gm.) every 3 days

		—19	189	6.10	3.1	1.7	68	45	23	...	104	72	1,580	3.7	54	EI	14 months after operation; thyroid ¼ grain (0.016 Gm.) three times a day
6	53	—37	133	5.85	2.3	1.4	55	41	32	...	130	86	2,200	3.3	61	A	4 months after operation
		—30	148	6.30	2.4	1.5	57	41	20	6.7	114	80	1,960	3.2	55	EI	18 months after operation; thyroid 1/10 grain (0.006 Gm.) daily
7	65	—36	160	6.35	2.5	1.2	46	35	21	4.1	138	90	1,890	3.9	85	A	10½ months after operation; thyroid 1/10 grain (0.006 Gm.) daily
8	57	— 3	163	5.95	2.7	2.0	73	38	18	8.0	160	90	1,100	4.7	64	A	Before operation
		—22	135	6.23	2.2	1.5	74	29	21	7.7	164	102	1,080	3.9	53	A	4 months after operation; no thyroid for 5 weeks
		—34	118	6.95	1.7	1.1	63	27	27	8.9	150	94	1,010	2.8	45	A	4½ months after operation; no thyroid for 7 weeks
		—13	149	6.23	2.4	1.7	78	31	..	...	140	90	1,100	3.8	48	EI	9 months after operation; thyroid 1/10 grain (0.006 Gm.) and 2/10 grain (0.012 Gm.) on alternate days
9	57	—11	184	5.00	3.7	2.1	68	54	18	6.0	160	100	1,100	6.5	96	A	Before operation
		—25	156	6.67	2.3	1.4	60	39	28	...	140	82	.....	3.4	57	A	6 weeks after operation
		—22	163	6.20	2.6	1.5	69	38	..	...	140	80	980	3.9	57	A	4 months after operation; thyroid 1/10 grain (0.006 Gm.) twice a day
10	59	— 4	230	6.15	3.8	2.0	73	52	16	8.1	150	100	1,450	6.5	89	EI	Before operation
		—18	197	6.10	3.2	1.7	73	44	21	6.6	132	84	.....	4.7	64	EI	3 months after operation; thyroid 1/10 grain (0.006 Gm.) daily
11	56	— 2	223	5.80	3.8	2.2	70	55	13	9.1	150	90	.....	6.2	89	EI	Before operation
		—17	180	6.10	2.9	1.6	58	50	17	7.7	150	90	.....	4.7	81	EI	8 weeks after operation

* A indicates measurements of the cardiac output by means of the acetylene method.
EI indicates such measurements made by means of the ethyl iodide method.

oxygen difference were made by the acetylene method of Grollman, Friedman, Clark and Harrison.[5] The values reported represent the average of two or more measurements made at the same level of basal metabolism. The maximum deviation from the average for any one value of the arteriovenous oxygen difference accepted as reliable was ± 7.7 per cent, and the average deviation from the values reported was ± 3.3 per cent. The minute volume output of the heart was calculated from the arteriovenous oxygen difference and the oxygen consumption, the latter being estimated from data obtained during the measurement of the basal metabolic rate. The venous pressure was then measured by the direct method of Moritz and von Tabora,[6] and finally the velocity of blood flow was estimated, the index used being the "arm to tongue" circulation time measured with decholin (sodium dehydrocholate).[7] The figures for the velocity of blood flow are the averages of two or more readings which did not differ from each other by more than two seconds. In three instances the velocity of blood flow was not measured on the same day as the cardiac output. The work of the left ventricle was calculated, the formula of Evans and Matsuoka[8] being used, $W = QR + (wV^2/2_g)$,[9] disregarding the velocity component $wV^2/2_g$, since it represents only from 1 to 3 per cent of the total work.

When the measurements of the cardiac output were made by the ethyl iodide method, the procedure was similar to that described, except that the basal metabolic rate was determined by the Tissot method simultaneously with the cardiac output. The values reported represent the average of two or more determinations of the cardiac output made at the same level of basal metabolism. The average deviation from the values reported was ± 4.9 per cent. In three instances values were accepted which differed from each other by slightly more than ± 10 per cent. It was felt that these values were valid, since they were in harmony with other values obtained on the same patients at other times. They were accepted, however, only because the basal metabolic rate in each instance was changing rapidly and no opportunity for further study at the same level of basal metabolic rate was available.

The results obtained by the ethyl iodide and the acetylene method on the same patients agree with each other within ± 5 per cent (tables 1 and 2). However, in our hands the ethyl iodide method was the more satisfactory of the two. It requires no period of training for the patient and no prescribed respiratory rate, rhythm and depth, so that determinations even on myxedematous patients are usually satisfactory. The only unreliable results obtained by this method occurred in patients with severe dyspnea and, in rare instances, in patients with marked myxedema, in whom the respirations were so extremely slow and shallow that satisfactory samples of alveolar air were not obtainable.

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7. Gargill, S. L.: The Use of Sodium Dehydrocholate as a Clinical Test of the Velocity of Blood Flow, New England J. Med. **209**:1089, 1933.

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9. W = work; Q = cardiac output per unit of time; R = arterial resistance (mean blood pressure × 13.6); V = velocity of blood in aorta; w = weight of blood; g = acceleration due to gravity.

TABLE 2.—*Data on Patients with Congestive Failure*

Case	Age, Years	Basal Metabolic Rate, Deviation from Normal, Percentage	Oxygen Consumption, Cc. per Minute	Arteriovenous Oxygen Difference, Volumes per Cent	Cardiac Minute Volume Output, Liters	Cardiac Index	Pulse Rate	Cardiac Output per Beat, Cc.	Blood Velocity, Arm to Tongue Circulation Time, Seconds	Venous Pressure, Cm. Water	Arterial Pressure, Systolic, Mm. Mercury	Arterial Pressure, Diastolic, Mm. Mercury	Vital Capacity, Cc. per Sq. Meter	Work per Minute, Kilogrammeters	Work per Beat, Grammeters	Comment
12	53	−20	199	7.28	2.8	1.4	69	40	36	5.4	110	80	2,100	3.6	52	27 months after operation
13	52	−30	160	7.81	2.1	1.2	66	31	41	4.4	130	90	1,800	3.1	48	2 years after operation
14	55	−34	145	6.72	2.1	1.3	59	36	31	0	168	102	1,720	3.9	65	2 years after operation
15	24	−31	158	7.00	2.3	1.3	51	44	58	5.5	108	70	2,100	2.8	54	2 years after operation; thyroid 1/10 grain (0.006 Gm.) daily
16	23	−25	190	7.41	2.6	1.4	63	41	45	9.5	110	70	1,380	3.2	50	21 months after operation; thyroid 1/10 grain (0.006 Gm.) daily
17	48	−14	207	5.90	3.6	1.9	69	52	26	6.7	180	120	1,100	7.3	106	13 months after operation; thyroid ¼ grain (0.016 Gm.) every 2 days
		−18	197	6.69	2.9	1.5	71	41	35	6.2	230	140	.....	7.3	103	18 months after operation; thyroid ¼ grain (0.016 Gm.) every 2 days
18	32	− 8	175	6.50	2.7	1.7	66	40	17	8.8	110	76	1,040	3.2	49	15 months after operation; thyroid 1/10 grain (0.006 Gm.) every 2 days
19	58	−34	163	6.86	2.4	1.3	53	45	..	...	150	90	1,650	3.9	74	7 months after operation
20	38	+ 1	268	8.84	3.0	1.6	51	60	42	10.6	120	70	1,600	3.9	64	Before operation
		− 7	245	7.34	3.3	1.7	58	57	31	6.0	115	60	.....	3.9	69	2 weeks after operation
		−21	192	8.07	2.4	1.3	52	46	43	7.0	110	60	1,800	2.8	53	3 weeks after operation
21	66	− 9	218	6.90	3.2	1.8	75	43	22	2.3	135	85	1,900	5.2	70	Before operation
		−15	185	8.25	2.2	1.3	70	32	29	1.0	138	85	1,800	3.7	52	10 days after operation
22	48	− 1	236	6.85	3.5	1.9	71	49	33	5.4	110	70	1,330	4.3	60	Before operation
		−12	217	7.03	3.1	1.7	71	43	44	3.1	100	70	.....	3.6	50	3 weeks after operation
		−20	201	7.69	2.7	1.4	64	43	59	7.5	105	70	.....	3.2	50	4 weeks after operation
		−27	179	8.18	2.3	1.2	55	41	53	8.5	105	70	1,240	2.7	50	5 weeks after operation
23	36	± 0	179	6.90	2.6	1.8	41	65	22	13.0	120	80	1,275	3.6	89	Before operation
		−19	151	7.90	1.9	1.3	38	33	26	10.0	120	80	1,275	2.6	68	2 weeks after operation

RESULTS

Cardiac Output and Work.—In the patients without congestive failure the cardiac output before operation was within normal limits, whereas in the patients with congestive failure it was at or somewhat

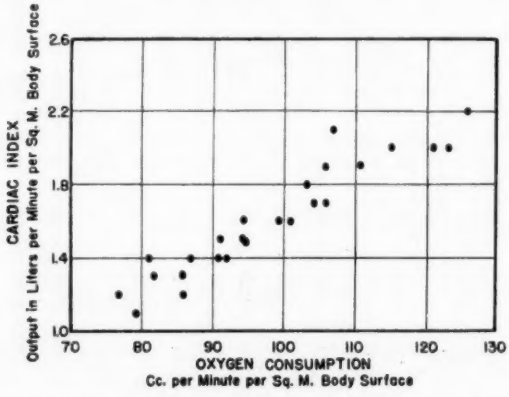

Fig. 1.—Relation between the oxygen consumption per square meter of body surface and the cardiac index in patients without congestive failure.

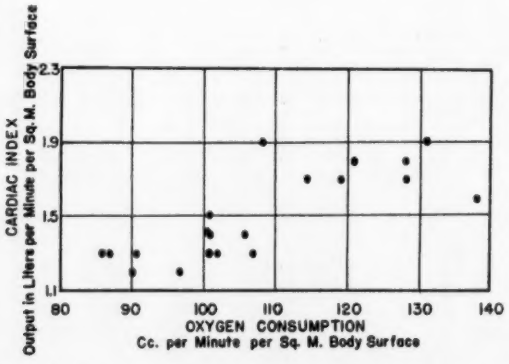

Fig. 2.—Relation between the oxygen consumption per square meter of body surface and the cardiac index in patients with congestive failure.

below the lower limit of normal. After total thyroidectomy the cardiac output was decreased in all twenty-three patients (tables 1 and 2; charts 1 and 2). When the basal metabolic rates decreased to between minus 25 and minus 37 per cent, the cardiac indexes (cardiac output in liters per square meter of body surface) fell to between 1.1 and 1.4

(table 1; chart 1), as compared to the normal values of 2.2 ± 0.3.[10] The output observed in cases 8, 9, 10, 11, 22 and 23 both before and after operation showed that as the basal metabolic rate falls the minute volume output of the heart decreases to a greater percental extent than does the oxygen consumption (table 3). The repeated measurements obtained in case 5, studied at various levels of basal metabolism after operation, also clearly exemplify this.

The work of the heart was diminished after operation in every instance but one and generally paralleled the cardiac output. In case 4 a slight increase in blood pressure occurred, which compensated for the fall in cardiac output, so that parallelism between the work of the heart and the decrease of metabolic rate was not close.

Arteriovenous Oxygen Difference.—An increase in arteriovenous oxygen difference was evident at low levels of metabolism (tables 1

TABLE 3.—*Percentage Decrease in Oxygen Consumption and Cardiac Output After Operation*

Case	Decrease in Oxygen Consumption, Percentage	Decrease in Cardiac Output, Percentage
8	22.4	25.0
	34.7	45.0
	14.1	15.0
9	15.0	33.3
	12.2	28.6
10	14.6	15.0
11	19.8	27.3
22	9.2	10.5
	19.1	26.4
	26.0	36.8
23	15.7	26.8

and 2; charts 3 and 4). The disproportionate decrease in cardiac output noted (table 3) was associated with this progressive increase in arteriovenous oxygen difference. Relatively minor changes in oxygen difference occurred when the basal metabolic rate had fallen to between minus 10 and minus 20 per cent. At lower levels of metabolism these changes were much more striking (charts 3 and 4). These changes in arteriovenous oxygen differences were most clearly seen in patients without congestive failure. In most cases the patients with congestive failure showed similar changes. In one instance (case 20), however, in which a high arteriovenous oxygen difference was found preoperatively, there was a temporary decrease soon after operation, followed by an increase.

Velocity of Blood Flow.—In the patients without congestive failure the velocity of blood flow was usually decreased when hypothyroidism

10. Grollman, A.: Physiological Variations in the Cardiac Output of Man: VI. The Value of the Cardiac Output of the Normal Individual in the Basal Resting Condition, Am. J. Physiol. **90**:210, 1929.

developed (table 1). In three of the twenty-three patients (cases 1, 4 and 11) the velocity of blood flow was not less than normal, although the cardiac output was strikingly decreased. In two other patients (cases 5 and 6) the changes in circulation time and cardiac output were not in proportion. In most instances, however, the changes in the velocity of

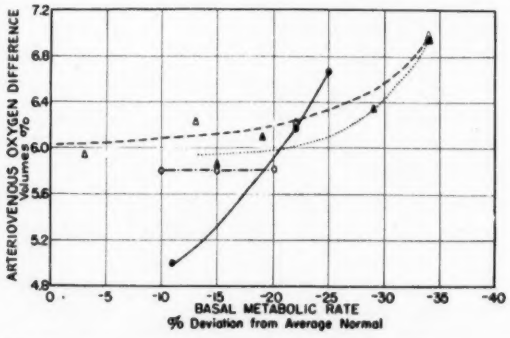

Fig. 3.—Relation between the arteriovenous oxygen difference and the basal metabolic rate in patients without congestive failure.

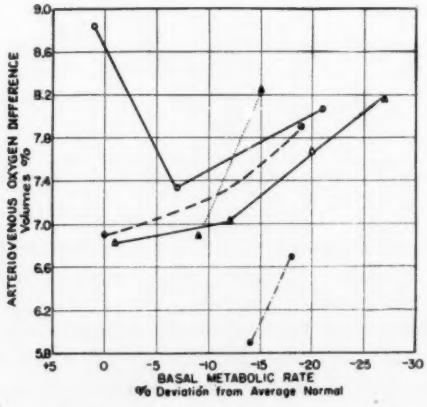

Fig. 4.—Relation between the arteriovenous oxygen difference and the basal metabolic rate in patients with congestive failure.

blood flow and in the minute volume output roughly paralleled each other.

The circulation time was very much increased in the patients with congestive failure even before operation (table 2). After operation the circulation time became still more slowed in ten instances; it was essentially unchanged in one case (case 20).

Venous Pressure, Arterial Pressure and Vital Capacity.—The venous and arterial blood pressures and the vital capacity showed no significant changes after total thyroidectomy in the patients without cardiac decompensation (table 1). No striking changes in arterial blood pressure or in vital capacity were found after operation (table 2) in patients with congestive failure. The same was true of the venous pressure in most instances; in the one case (case 20) in which the venous pressure was slightly elevated before operation a decrease to within normal limits occurred postoperatively. In the other patients the venous pressure before operation was within normal limits, the patient having received prolonged medical treatment in order to achieve the most favorable physical condition possible preoperatively.

COMMENT

A high coefficient of correlation between the cardiac output and the basal oxygen consumption in normal persons has been demonstrated by Starr, Collins and Wood.[11] However, the studies of Bock and Field [12] on two patients with spontaneous myxedema showed that at low levels of metabolism the cardiac output is disproportionately decreased. The results of the present study demonstrate a similarity in this respect between spontaneous and induced hypothyroidism.

The disproportionate decrease in cardiac output observed by us in persons with hypothyroidism developing subsequent to total thyroidectomy is accompanied by an increase in arteriovenous oxygen difference. The latter increase first becomes evident when the basal metabolic rate has fallen to between minus 15 and minus 20 per cent and becomes progressively greater as the basal metabolic rate decreases below this level.

In one patient with congestive failure the arteriovenous oxygen difference was elevated before operation. This is a common finding in patients with congestive failure. In such patients the arteriovenous oxygen difference tends to return to normal as compensation is improved. In the patient just mentioned (case 20) a decrease in arteriovenous oxygen difference occurred shortly after operation, indicating an improvement in cardiovascular function. Subsequently the effect of the induced hypothyroidism became dominant and the arteriovenous oxygen difference increased.

The cause of the increased arteriovenous oxygen difference noted in hypothyroidism has not been determined. The increased arteriovenous difference is not to be regarded as evidence of heart failure due to

11. Starr, I., Jr.; Collins, L. H., and Wood, F. C.: Studies of the Basal Work and Output of the Heart in Clinical Conditions, J. Clin. Investigation **12**:13, 1933.

12. Bock and Field, cited by Means.[1]

"myxedema heart," since it occurred in patients with cardiac decompensation when the signs of congestive failure were disappearing instead of increasing (cases 20, 21 and 22). The fact that the venous pressure was not elevated in our patients with marked hypothyroidism is additional evidence that the circulatory changes were not due to cardiac decompensation. Estimation of the size of the heart on roentgen examination in fifteen of the patients before and after operation, furthermore, revealed enlargement after the development of hypothyroidism in only five, while in two of the patients with congestive failure (cases 12 and 15) the size of the heart actually decreased. The significance of such changes has been discussed elsewhere.[13]

It is of interest that in patients with hypothyroidism there is an increase in arteriovenous oxygen difference, while in patients with an elevation of the metabolic rate due to exophthalmic goiter the oxygen difference is usually decreased,[14] since the cardiac output is increased more than the oxygen consumption. It has been suggested [14e] that the changes in the cardiac output and the oxygen difference which occur in exophthalmic goiter are related in some way to the presence of increased amounts of thyroid hormone in the blood stream. However, in one of our patients (case 11), with hyperthyroidism but with a normal basal metabolic rate, a normal arteriovenous oxygen difference was found; this suggests that the arteriovenous difference is related to the level of metabolism rather than to the degree of activity of the thyroid gland. The changes in arteriovenous oxygen difference observed in patients with disorders of metabolism may be considered as manifestations of vasomotor readjustments which are designed to maintain a normal internal body temperature, the decreased arteriovenous oxygen difference associated with the elevation of metabolism usually found in exophthalmic goiter being due to an abnormally rapid flow of blood to the lungs and skin in an attempt to throw off the excessive heat produced in this condition. Conversely, the increased oxygen difference of hypothyroidism may be an attempt to conserve heat.

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13. Davis, D.; Weinstein, A. A.; Riseman, J. E. F., and Blumgart, H. L.: Treatment of Chronic Heart Disease by Total Ablation of the Thyroid Gland: VII. The Heart in Artificial Myxedema, Am. Heart J. **10**:17, 1934.

14. (*a*) Liljestrand, G., and Stenström, N.: Clinical Studies on the Work of the Heart During Rest: I. Blood Flow and Blood Pressure in Exophthalmic Goiter, Acta med. Scandinav. **63**:99, 1925. (*b*) Robinson, G. C.: The Measurement of the Cardiac Output in Man and Its Variations, J. A. M. A. **87**:314 (July 31) 1926. (*c*) Lauter, S.: Ueber den Kreislauf bei Basedow, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **40**:292, 1928. (*d*) Fullerton, C. W., and Harrop, G. A.: The Cardiac Output in Hyperthyroidism, Bull. Johns Hopkins Hosp. **46**:203, 1930. (*e*) Boothby, W. M., and Rynearson, E. H.: Increase in Circulation Rate Produced by Exophthalmic Goiter Compared with That Produced in Normal Subjects by Work, Arch. Int. Med. **55**:547 (April) 1935. Means.[1a] Bansi and Groscurth.[1e]

Calculations from the data obtained in the present study show that the work of the left ventricle diminishes as the basal metabolic rate decreases after total thyroidectomy. At levels of metabolism below minus 15 to minus 20 per cent, the work of the heart is reduced more than the oxygen consumption, a reduction of 30 per cent in the oxygen consumption being associated with a decrease of 40 per cent in the cardiac work. In every patient studied before and after operation the reduction in the work of the heart was associated with clinical improvement. Blumgart and his co-workers [2] have advanced the concept that the relief obtained in congestive failure and in angina pectoris after total thyroidectomy is due to lessened demands on the heart resulting from the decreased oxygen consumption in hypothyroidism. Our observations support this concept and show, moreover, that the diminution in the work of the heart at low levels of metabolism even exceeds the reduction in oxygen consumption.

In patients operated on for angina pectoris, relief is due to reduction of the work of the heart to or below an amount which it can do without the development of anoxemia. Diminution of the output of the left ventricle does not affect the coronary blood flow appreciably;[15] so the nutrition of the myocardium is not impaired by the reduction of cardiac output which follows total thyroidectomy.

In the patients with congestive failure the lowest basal cardiac index observed before operation was 1.6 (table 2). After total thyroidectomy, when the basal metabolism had decreased to hypothyroid levels, the cardiac index was reduced to between 1.2 and 1.4 in all cases (table 2). Thus, in patients with congestive failure the basal oxygen consumption after total thyroidectomy falls well below the point at which it merely balances the low cardiac output and the cardiac output at rest coincidentally becomes reduced below the preoperative level. This makes it possible for the cardiac output in such patients to increase appreciably in response to work, so that the degree of activity may be increased without discomfort. In addition, a significant measure of rest is afforded the heart in the patients with angina pectoris as well as in those with congestive failure as a result of the marked diminution in basal cardiac work which occurs after operation.

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15. Anrep, G. V., and Segall, H. N.: Regulation of the Coronary Circulation, Heart **13**:239, 1926 Anrep, G. V., and Hausler, H.: The Coronary Circulation: I. The Effect of Changes of the Blood Pressure and of the Output of the Heart, J. Physiol. **65**:357, 1928. Anrep, G. V.; Davis, J. C., and Volhard, E.: The Effect of Pulse Pressure upon the Coronary Blood Flow, J. Physiol. **73**:405, 1931. Rein, H.: Die Physiologie der Herz-Kranzgefässe: I. Mitteilung, Ztschr. f. Biol. **92**:101, 1932. Anrep, G. V., and Saalfeld, E. F.: The Effect of the Cardiac Contraction upon the Coronary Flow, J. Physiol. **79**:317, 1933.

SUMMARY AND CONCLUSIONS

Data on the changes in the cardiac output and related aspects of the circulation after total thyroidectomy in twenty-three patients are presented.

The output in volume per minute and the work of the heart are greatly diminished in hypothyroidism following total ablation of the normal thyroid gland.

The cardiac output decreases progressively to a greater extent than the oxygen consumption as the basal metabolic rate falls in hypothyroidism. This disproportionate decrease in cardiac output is accompanied by a progressive increase in the arteriovenous difference. These changes are most striking when the basal metabolic rate has fallen below minus 15 to minus 20 per cent.

In nineteen of twenty-three patients the velocity of blood flow was slowed when the cardiac output was low. In patients with congestive failure the velocity of blood flow was much slower than in those without congestive failure. In three instances the velocity of blood flow did not reflect accurately the work of the heart.

The venous pressure, arterial pressure and vital capacity were not significantly altered after total thyroidectomy in the patients in this series.

The measurements obtained for the same patients by the acetylene and ethyl iodide methods are compared. The results are the same by the two methods under the conditions of the experiments described.

Reduction in the work of the heart was associated with clinical improvement in the patients studied.

The data obtained in this study are in harmony with the concept that the relief obtained after operation in patients with angina pectoris is due principally to reduction of the work of the heart to or below an amount which it can do without the development of anoxemia.

In patients with congestive failure the basal oxygen consumption after total thyroidectomy falls well below the point at which it merely balances the low cardiac output, and the cardiac output at rest coincidentally becomes reduced below the preoperative level. This makes it possible for the cardiac output in such patients to increase appreciably in response to work, so that the degree of activity may be increased without discomfort.

In addition, the marked diminution in basal cardiac work which occurs in all patients after operation affords the heart a significant measure of rest.

LIVER THERAPY FOR COMBINED SCLEROSIS

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The experimental work of Whipple and his associates on anemia, leading to the clinical application of liver therapy by Minot and Murphy in 1926, is one of the brilliant chapters of achievement in American medicine. Owing to these researches physicians are now able better to understand and control the disease of the blood classified as pernicious anemia. One of the serious complications of this condition is a degenerative process of the spinal cord designated as combined sclerosis because of the pathologic areas of gliosis resulting from degenerative processes in the most involved portions of the cord, the posterior and lateral fiber tracts. A far better nomenclature for this disease is subacute myelinic degeneration, for the fibers in the brain may also be involved, and there is evidence of involvement of the myelin sheaths of the peripheral nerves as well.

The neural complications may be present without appreciable anemia and may not be present with a high degree of anemia, while they are rarely seen with secondary anemia. The neural degenerations cannot, therefore, logically be attributed to the anemia itself. The prevailing theory is that there is a deficiency factor in pernicious anemia which determines the blood picture and the neural degenerations and which may be emphasized in the blood, in the nervous system or in both. This deficiency has been designated as a lack of the antianemic liver fraction G of Cohn, which is absent from the livers of patients with pernicious anemia not treated with liver.

The clinical and pathologic manifestations of subacute myelinic degeneration were described in a paper [1] read before the Section of Neuropsychiatry of the State Medical Society in 1917, in a report of 23 cases with 4 necropsies, and since then little has been added to the knowledge of the physical characters of this disorder. It is a relatively frequent

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Read before the Section of Neuropsychiatry at the Sixty-Fourth Annual Session of the California Medical Association, Yosemite National Park, Calif., May 15, 1935.

1. Schaller, W. F.: Spinal Cord Changes in Combined Sclerosis, California State J. Med. **16**:44 (Jan.) 1918.

neurologic condition, statistics showing an incidence approximately four times that of multiple sclerosis. Before the introduction of liver therapy efforts to combat neural complications were discouraging in the extreme, and the disease invariably progressed; since liver therapy was introduced, in our experience there has been a dramatic change in response to treatment. Reports on the results of liver therapy in patients with neurologic complications of pernicious anemia have been variable; favorable publications are notably those of Minot and Murphy,[2] Bubert,[3] Mason,[4] Davidson, McCrie and Gullard,[5] Fried,[6] Richardson,[7] Ungley and Suzman,[8] Lottig,[9] Farquharson and Graham,[10] Schilling,[11] Starr,[12] Strauss and Castle,[13] Baker, Bordley and Longcope[14] and Meulengracht.[15]

Bubert reported a case in which there was a steady downward course before the institution of liver therapy in 1926; liver therapy and the maintenance of a sustained red blood cell count of over 5,000,000 for nine months resulted in a marked improvement in the neurologic status. Richardson emphasized the necessity of keeping the red blood cell count above 4,500,000 in order to prevent involvement of the nervous system.

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2. Minot, G. R., and Murphy, W. P.: A Diet Rich in Liver in the Treatment of Pernicious Anemia: Study of One Hundred and Five Cases, J. A. M. A. **89**:759 (Sept. 3) 1927.

3. Bubert, H. M.: Subacute Combined Sclerosis, J. A. M. A. **90**:903 (March 24) 1928.

4. Mason, E. H.: Pernicious Anemia, J. A. M. A. **90**:1527 (May 12) 1928.

5. Davidson, G.; McCrie, J. G., and Gullard, G. L.: The Treatment of Pernicious Anemia: Liver Diet, Lancet **1**:847, 1928.

6. Fried, B. M.: Subacute Combined Degeneration of the Spinal Cord in Pernicious Anemia, J. A. M. A. **92**:1260 (April 13) 1929.

7. Richardson, E.: Pernicious Anemia, New England J. Med. **200**:540, 1929.

8. Ungley, C. C., and Suzman, M. M.: Subacute Combined Degeneration of the Cord: Symptomatology and Effects of Liver Therapy, Brain **52**:271 (Sept.) 1929.

9. Lottig, Heinrich: Zur Frage der Beeinflussung der Rückenmarks-Erkrankung bei Biermerscher Anämie durch Leberdiät, München. med. Wchnschr. **77**:858 (May 16) 1930.

10. Farquharson, M. B., and Graham, D.: Liver Therapy in the Treatment of Subacute Combined Degeneration of the Cord, Canad. M. A. J. **23**:237, 1930.

11. Schilling, V.: Gänsslens injizierbares Leberextrakt, Klin. Wchnschr. **10**: 301 (Feb. 14) 1931.

12. Starr, P.: The Prevention of Spinal Cord Degeneration in Pernicious Anemia, J. A. M. A. **96**:1219 (April 11) 1931.

13. Strauss, M. B., and Castle, W. B.: Parenteral Liver Therapy in the Treatment of Pernicious Anemia, J. A. M. A. **98**:1620 (May 7) 1932.

14. Baker, B. M.; Bordley, J., and Longcope, W. T.: The Effect of Liver Therapy on the Neurologic Manifestations of Pernicious Anemia, Am. J. M. Sc. **184**:1, 1932.

15. Meulengracht, E.: Verhütung und Behandlung der Rückenmarksstörungen bei perniziöser Anämie, Klin. Wchnschr. **12**:1163 (July 29) 1933.

In Starr's patients whose red blood cell count was kept above 5,000,000 progressive degeneration of the nervous system did not occur. Baker, Bordley and Longcope stated that although the correlation between improvement in the neurologic status and the blood picture is not absolute, it is noticeable that patients showing marked improvement usually have a high red cell count. Improvement in 58.93 per cent of signs and symptoms was found in their patients who were treated for more than ten months. A number of patients were given 10 pounds (4.5 Kg.) of liver weekly (650 Gm. daily or its equivalent in powdered extract). The necessity for long continued intensive treatment is emphasized. There has recently appeared a significant article by Strauss and his co-workers [16] concerned only with changes referable to the spinal cord in patients observed for an average period of three years. Twenty-six patients were selected who had spasticity, ataxia or both, resulting in definite disturbances of locomotion signifying at least moderately severe degeneration in the cord. Eight of these patients showed unfavorable progress during oral administration of liver in amounts possible for them to ingest but responded favorably to parenteral administration of liver preparations equivalent in hematopoietic effectiveness to still greater quantities of orally administered material. The authors therefore emphasized the greater effectiveness of parenteral treatment, attributed to larger equivalent amounts than may be given orally, and called attention to the fact that patients receiving oral treatment should be carefully observed for the development of symptoms or signs relative to the nervous system. Patients with distinct neurologic lesions should be given parenteral therapy at once. In their study the "initial status" was evaluated only after the red blood cells numbered 3,500,000 per cubic millimeter. The average count was 4,300,000, and in the final neurologic status the count was 4,780,000. In the series 58 per cent of all abnormal signs encountered in the 26 patients remained unchanged; 17 per cent disappeared, and 25 per cent were improved. Treatment for all patients consisted of the intramuscular injection of solution of liver extract [17] in a minimum dose of 10 cc. once every three weeks. In commencing treatment of a previously untreated patient the usual procedure was to inject 10 cc. of the extract every three or four days during the first two to three weeks and then to give weekly injections of the same amount for the remainder of the first year. The dose was equivalent to about 50 per cent more than the amount taken by mouth by many patients. Strauss and his co-workers expressed the belief that

16. Strauss, M. B.; Solomon, P.; Schneider, A. J., and Patek, A. J.: Subacute Combined Degeneration of the Spinal Cord in Pernicious Anemia, J. A. M. A. **104**:1587 (May 4) 1935.

17. Liver extract-Lilly (N. N. R.) was used for oral administration, and solution of liver extract-Lilly (N. N. R.), for intramuscular administration.

disagreement in the literature often arises from the fact that results were recorded over too brief periods for adequate treatment to demonstrate its full effect.

The foregoing writers, therefore, stressed the importance of a high red cell count and of its maintenance over a considerable period.

Some writers have either doubted or denied a specific action of liver therapy against neurologic complications. We shall briefly review and analyze these adverse reports.

DISSENTING OBSERVATIONS ON BENEFICIAL EFFECTS OF LIVER THERAPY IN CONTROLLING NEURAL MANIFESTATIONS

The earliest adverse reports, notably those of Sturgis, Isaacs and Smith,[18] Cohen,[19] McAlpine,[20] Seyderhelm,[21] Curschmann,[22] Krause,[23] and Carey,[24] represent conclusions based on the lack of either adequate treatment from the point of view of the blood picture or the maintenance of a normal blood picture for a reasonable length of time. Sturgis and his co-workers used powdered liver extract; they reported 28 cases in 1927. The equivalent of 1 pound (453 Gm.) of liver was given daily, and in some cases as much as 1½ pound (680 Gm.) of liver was given; this was reduced to ½ pound (227 Gm.) when a convincing rise in the number of red blood cells had occurred. They stated that improvement in signs and symptoms does not parallel the improved blood pictures. The red blood cell counts were relatively high in the cases they reported, but the longest periods of treatment reported were one hundred and seventeen and one hundred and three days, respectively. It is apparent from later experience that adequate doses were not maintained for a sufficient period to justify the formulation of a definite opinion as to course and prognosis.

Smithburn and Zerfas [25] in 1931 reported on a group of 35 patients showing neurologic involvement in a total series of 115 patients with

18. Sturgis, C. C.; Isaacs, R., and Smith, M.: The Treatment of Pernicious Anemia with Liver Extract, Ann. Int. Med. **1**:994, 1927.

19. Cohen, A. E.: Subacute Combined Sclerosis, Progressive During Remission of Pernicious Anemia, J. A. M. A. **90**:1787 (June 2) 1928.

20. McAlpine, Douglas: A Review of the Nervous and Mental Aspects of Pernicious Anemia, Lancet **2**:643 (Sept. 28) 1929.

21. Seyderhelm, R.: Möglichkeiten und Grenzen der Lebertherapie, Deutsche med. Wchnschr. **55**:1704 (Oct. 11) 1929.

22. Curschmann, Hans: Die Nervenstörungen der Biermerschen Anämie und die Lebertherapie, Med. Klin. **25**:1767 (Nov. 15) 1929.

23. Krause, F.: Ueber das Versagen der Lebertherapie bei den funikulären Erkrankungen der perniziösen Anämie, Klin. Wchnschr. **8**:2177 (Nov. 19) 1929.

24. Carey, J. B.: Pernicious Anemia with Fatal Termination During a Liver Diet, Arch. Int. Med. **47**:893 (June) 1931.

25. Smithburn, K. C., and Zerfas, L. A.: Neural Symptoms and signs in Pernicious Anemia, Arch. Neurol. & Psychiat. **25**:1100 (May) 1931.

pernicious anemia. They administered fractions of liver deemed adequate to maintain what they designate a normal blood level. Three of the 35 cases were detailed by the authors: In case 1 the highest red cell count mentioned was 4,300,000; in case 2, in which the disease was reported to progress while treatment was given, the erythrocyte count at no time reached 4,000,000, and in case 3 the only mention of results of treatment was that the blood count returned to "normal." Smithburn and Zerfas' conclusions were that neurologic changes may develop or steadily progress while the patient is receiving daily amounts of liver adequate to maintain a normal erythrocyte level. This report obviously cannot be seriously considered as one dealing with a group of patients adequately treated by therapy controlling the erythrocyte count.

Carey stated that by adequate "is meant an amount found in other patients so treated that will keep the blood count and hemoglobin up to reasonable normal levels." The highest count in any of his patients is reported as 3,850,000. Of Sargent's [26] 4 patients, the only one who had a normal blood count was objectively improved. Ahrens,[27] without choosing to draw conclusions as to the efficacy of liver, stated that the maintenance of a high hemoglobin content and a red cell count of 5,000,000 does not prevent or improve changes in the cord, and he called attention to 3 cases in his series as proof of this contention; however, a review of these cases is not convincing, as regards either the maintenance of the blood picture or the duration of treatment. Fahr [28] made necropsies on 13 patients with pernicious anemia treated with liver in whom degeneration in the cord was found. He spoke of a hypothetic toxic condition determining organic changes independent of the condition of the blood. Davison [29] reported on 7 necropsies of patients treated with liver and compared the pathologic observations with those on untreated patients. He stated: "Histopathologically, all the treated patients showed progressive or glial changes (gliosis). These changes were not observed in the untreated patients with subacute combined degeneration. The myelin sheaths and axis cylinders were not influenced by the liver therapy." The gliosis might well be considered a reparative process not found in untreated patients.

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26. Sargent, W.: Treatment of Subacute Combined Degeneration of the Cord by Massive Iron Dosage, Lancet **1**:230 (Jan. 30) 1932.

27. Ahrens, R. S.: Neurologic Aspects of Primary Anemia, Arch. Neurol. & Psychiat. **28**:92 (July) 1932.

28. Fahr, T.: Pathologisch-anatomische Beiträge zur Kritik der Lebertherapie bei der perniziösen Anämie, Deutsche med. Wchnschr. **57**:8 (Jan. 2) 1931.

29. Davison, C.: Subacute Combined Degeneration of the Cord: Changes Following Liver Therapy; a Histopathologic Study, Arch. Neurol. & Psychiat. **26**: 1195 (Dec.) 1931.

Grinker and Kandel [30] concluded that liver therapy is not efficacious in improving or preventing degeneration in the central nervous system complicating pernicious anemia and that in the majority of cases the disease progresses slowly, no matter what therapy is employed. They made the pertinent observation that changes in neurologic signs may be falsely interpreted and that weakness may imitate damage in the cord. They further made the excellent point that well controlled neurologic observations are essential to an evaluation of the actual neural status during treatment. They studied a series of 50 patients over a period of two and a half years and defined adequate treatment as a quantity of liver sufficient to maintain a normal blood level, associated with the feeling of well-being peculiar to health. Their dose averaged the equivalent of 1 pound (453 Gm.) of liver a day in the form of domestic extract. The results in 37 patients who received treatment were analyzed. In 19 there was no change in neurologic status; in 10 the condition progressed under therapy; 4 showed apparent improvement, and 4 showed definite improvement. Two patients in the series received liver parenterally. In only 5 did the stated blood count attain normal accepted standards. In 1 patient (case 30) lost inferior tendon reflexes returned during the period of treatment, whereas other neurologic signs remained the same; the failure of deep sensation to return was interpreted as progression of the involvement in the lateral tracts; in 1 patient (case 29) inferior tendon reflexes were lost during the period of treatment.

Goldhamer and his co-workers [31] reported a high incidence (89.2 per cent) of involvement of the nervous system in a series of 461 patients with pernicious anemia. A level of 4,000,000 red cells was considered as an index of reasonable treatment. Of the patients who received adequate treatment, in 2 per cent the signs referable to the spinal cord were improved; in 83 per cent they were unimproved, and in 15 per cent they were aggravated. Of those who received inadequate treatment, improvement of signs referable to the cord occurred in 2 per cent; no improvement was noted in 59 per cent, and the signs became worse in 39 per cent. Improvement in symptoms was observed in less than 50 per cent of the patients. Goldhamer and his co-workers concluded that antianemic therapy does not have a specific curative effect on degeneration in the spinal cord but contributes only indirectly to improvement in the manifestations referable to such degeneration.

30. Grinker, R. R., and Kandel, E.: Pernicious Anemia: Results of Treatment of the Neurologic Complications, Arch. Int. Med. **54**:831 (Dec.) 1934.

31. Goldhamer, S. M.; Bethell, F. H.; Isaacs, R., and Sturgis, C. C.: The Occurrence and Treatment of Neurologic Changes in Pernicious Anemia, J. A. M. A. **103**:1663 (Dec. 1) 1934.

ADEQUATE THERAPY

Adequate therapy may be defined as the kind and amount of administration of a given remedy required to achieve a desired result with a strict control of the potency of the preparation and the regularity of its administration. Any physician who has had extensive experience with oral liver therapy cannot but be impressed with the difficulty of keeping patients to the faithful observance of prescribed dosage, by reason of the distaste and ennui incidental to ingestion of large amounts of liver. Because of this practical objection, liver extract was prepared in powdered form, and in 1931 a soluble extract became available for parenteral administration. These preparations have been standardized to correspond with whole liver, of which 225 Gm. daily has been estimated as the average maintenance dose in cases of pernicious anemia. When the central nervous system is involved one is faced with a situation comparable to that in cases of neurosyphilis, in which protracted and specialized forms of treatment and, as a rule, dosage far in excess of that required in systemic syphilis are required. Oral administration of liver may not be wholly effective or may be impracticable. Parenteral injections of higher potency have been available only in the recent past. Another important consideration of an adequate therapy is the response of the blood. There is frequent reference in the literature to blood values deemed as satisfactory responses to therapy which are far below normal standards. Williamson [32] designated the following numbers of red cells as normal for adults between the ages of 21 and 70 years: males, 5,180,000; females, 4,800,000. It is not solely a rational procedure but a responsible obligation on the part of the physician to endeavor to attain a normal red cell count and a high hemoglobin content; in fact, the level for both should be higher than normal in order to provide an overcompensatory effect in cases in which the condition is refractory. A strict observance of this requirement was emphasized in the discussion on this subject at the session of the American Medical Association in Milwaukee in 1933 before the Section on Nervous and Mental Disease by William P. Murphy. A recent personal communication from this high authority is to the effect that "if the blood is maintained at a normal level, neurologic changes do not start; they do not progress, and they are improved in 100 per cent of instances."

As our experience and convictions are at variance with those of writers who have disclaimed a specific action on the neural complications of pernicious anemia, we have recently reviewed our records of instances of neurologic complications in cases of this disease and have

32. Williamson, C. S.: Influence of Age and Sex on Hemoglobin, Arch. Int. Med. **18**:505 (Oct.) 1916.

selected 1931 as the date from which more effective preparations were available for treatment. Forty cases were reviewed. It was at once apparent that in only a small number of cases in this series were there fulfilled the requirements of a sustained, adequate therapy under control of the blood picture and neurologic status. It is to be emphasized, in accord with Grinker's statement, that the neurologic record should be considered of equal importance with the blood picture. Each blood count should be checked by a neurologic examination—subject to a double check, as it were.

REPORT OF CASES

The patients are divided in two groups. The first group includes patients adequately treated for an appreciable period of time and having a normal blood count (Williamson); the second group includes patients observed for considerable periods of time receiving therapy not fully conforming to the standard of sustained, controlled, adequate treatment but showing a satisfactory neurologic status and occupational activity.

Group 1.—This group comprises 5 cases.

CASE 1 (Observed for Six Years).—A 67 year old retired insurance man was seen in the medical clinic on Feb. 18, 1929; he complained of constipation, gas and anorexia. Physical examination gave normal results except for papillary atrophy of the tongue and some loss of vibratory sensation in the lower extremities. Laboratory examination showed a lack of free hydrochloric acid in the gastric contents, a red cell count of 2,400,000, 60 per cent hemoglobin, a color index of 1.25 and moderate poikilocytosis and anisocytosis. A diagnosis of pernicious anemia was made, and the patient was instructed to eat 225 Gm. of whole liver daily. By May 3, 1929, his red cell count had risen to 4,000,000 and his hemoglobin content to 78 per cent, and there was a great increase in his feeling of well-being. He complained of the amount of liver he was required to eat, and on Oct. 7, 1929, the treatment was changed to two vials of liver extract [17] daily. This regimen maintained his red cell count at approximately 4,000,000 until Oct. 30, 1930, when he first complained of numbness in the hands and legs. Examination at this time by Dr. Henry Newman gave the following results: Romberg sign, positive; coordination in the arms, poor; deep reflexes, equal and active; pyramidal tract reflexes, present, and vibratory sensation, impaired below the waist and almost absent below the knees. The patient was hospitalized and received ten hyperpyrexia baths. The dose of liver was increased to three vials of liver extract [17] and ¼ pound (113 Gm.) of whole liver daily. He also received injections of nonspecific protein. In spite of this treatment, which maintained his red cell count at an average of 4,000,000, he complained of progressive weakness, and in December 1931 was again hospitalized. His blood count showed 3,650,000 red cells and 79 per cent hemoglobin. Reexamination by Doctor Newman showed inability to walk without assistance, spastic and ataxic gait, incoordination of the arms and legs, equal deep reflexes, positive Babinski, Gordon and Oppenheim signs bilaterally, patellar clonus, and further diminution of vibratory sensation. He was given twenty-four vials of liver extract [17] by stomach tube, but no reticulocyte response occurred in nine days. After this he received eight intramuscular injections of solution of liver extract [17] of 10 cc. each. He was dismissed to the clinic,

where he received injections of 8 cc. of liver extract three times a week. By Feb. 15, 1932, his red cell count was 4,700,000 and his hemoglobin content 89 per cent; he felt much improved and was able to attend the clinic by himself. On March 9, 1932, his red cell count was 5,000,000 and his hemoglobin content 84 per cent, and under the aforementioned regimen the blood picture was maintained close to that level. On Feb. 20, 1933, he entered the hospital for a check-up. His red cell count was 5,100,000 and his hemoglobin content 95 per cent. Examination by the house physician showed slightly spastic and ataxic gait, active and equal deep reflexes, absence of signs referable to the pyramidal tract and a questionable Romberg sign. The patient continued to receive treatment in the clinic as before, and on July 20, 1934, the dose of liver extract was reduced to 10 cc. administered intramuscularly twice weekly. He complained, however, of not feeling up to par, and on Sept. 18, 1934, his red cell count had fallen to 3,980,000. He was therefore

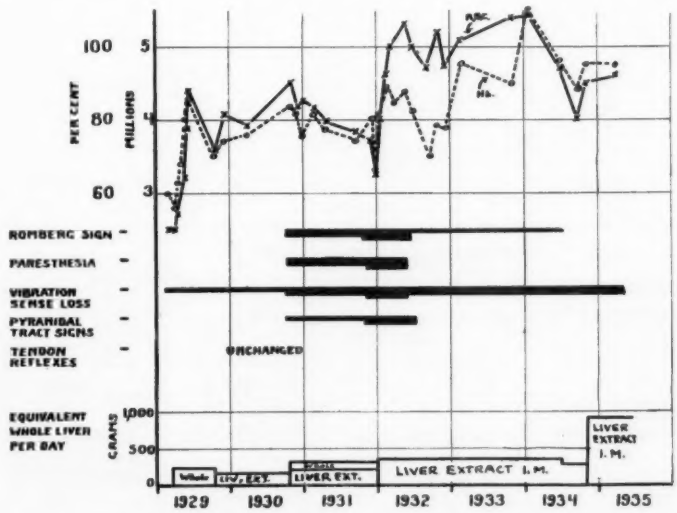

Fig. 1 (case 1).—Graphic representation of results of liver therapy. From 1929 to 1931, inclusively, the patient received liver extract [17] orally; from 1932 to October 1934 he received liver extract [17] intramuscularly, and during the remaining period of treatment, concentrated solution of liver extract [33] intramuscularly.

given 10 cc. of liver extract intramuscularly three times weekly, and on October 26 his count had risen to 4,500,000. At this time treatment was changed to intramuscular injections of 5 cc. of concentrated solution of liver extract [33] twice weekly. On March 12, 1935, his red cell count was 4,530,000 and his hemoglobin content 87 per cent. Examination by Doctor Newman showed normal gait, a negative Romberg sign, good coordination, active and equal reflexes, absence of clonus and of pyramidal tract signs and diminution but not absence of vibratory sensation in the legs.

33. Solution of liver extract concentrated-Lilly (N. N. R.) was used.

Case 2 (Observed for Two Years).—An American dressmaker, aged 52, was hospitalized on March 10, 1933; she presented a neurologic condition of dysesthesias, impairment in vibratory sensation below the knees, unsteady gait, active reflexes throughout without pathologic signs referable to the pyramidal tract and a negative Romberg sign. The red cell count was 2,500,000 and the hemoglobin content 60 per cent. There was no free hydrochloric acid in the stomach contents. The patient was given 10 cc. of solution of liver extract [17] intramuscularly for seven consecutive days and thereafter three weekly injections of the same amount of that preparation until December 1933, when the dosage was reduced to weekly injections, which were continued throughout 1934. Then 3 cc. of a solution of liver extract [34] was injected weekly. In March, April and May of 1934 there was a complicating diarrhea which followed ingestion of liver and bacon. In August the medication was supplemented by three capsules of extralin daily. On

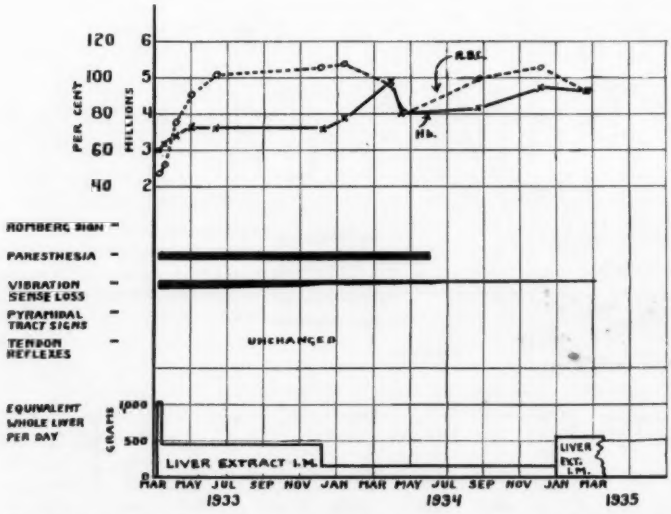

Fig. 2 (case 2).—Graphic representation of results of liver therapy. From March 1933 to January 1935 the patient received liver extract,[17] and from January to March 1935, another preparation [34] of liver extract.

June 16, 1933, the blood count showed 5,100,000 red cells and 72 per cent hemoglobin; it rose to 5,400,000 red cells and 78 per cent hemoglobin in January 1934. In April it fell to a low level of 4,000,000 red cells and 80 per cent hemoglobin at the period of the gastro-intestinal upset. In September 1934 the red blood cell count rose to 5,000,000 and the hemoglobin content to 84 per cent, and in December the level reached 5,280,000 and 95 per cent, respectively. The last examination of the blood, in February 1935, showed 4,530,000 red cells and 92 per cent hemoglobin. In May 1933 vibratory sensation was improved in both legs;

34. Lederle solution of liver extract parenteral refined and concentrated (N. N. R.) was used.

in April 1934 Doctor Bloomfield stated, "There is still some impairment of vibratory sensation, but the function seems to be better than a year ago." In March 1935 vibratory sensation was not diminished. The negative signs remained so and the tendon reflexes were unchanged. In June 1934 the patient still complained of slight numbness in the extremities and of unsteadiness.

Case 3 (Observed for Thirteen Months).—An American housewife, aged 49, entered the Lane Hospital in August 1932, complaining of numbness of the hands and feet which had been present for eleven months. Examination showed a positive Romberg sign, unsteady gait, hyperactive knee and ankle jerks, a positive Babinski sign bilaterally and absence of vibratory sensation from the iliac crests down. The red blood cells numbered 2,900,000, and the hemoglobin content was 74 per cent. Analysis of the gastric contents showed no free hydrochloric acid.

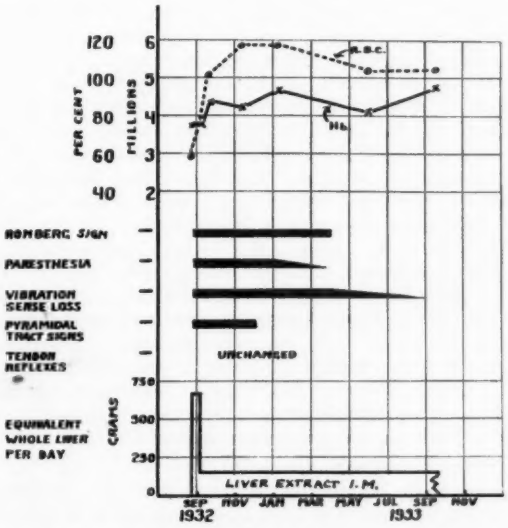

Fig. 3 (case 3).—Graphic representation of results of liver therapy. The patient received liver extract.[17]

Therapy was started by intensive intramuscular injections of solution of liver extract;[17] 90 cc. was administered over a period of fourteen days, producing a prompt reticulocyte response and an increase of 1,000,000 red cells. Thereafter the dose was reduced to 10 cc. weekly. In September 1932 the red cells numbered 5,100,000 and the hemoglobin content was 87 per cent; in November the red cell count was 5,900,000 and the hemoglobin content 84 per cent. In December 1932 examination by Dr. Henry Gibbons gave the following results: vibratory sensation, present at ankles but very faint; Babinski sign, negative; Romberg sign, 2 plus; gait, slightly unsteady. In January 1933 the red cells numbered 5,900,000 and the hemoglobin content was 93 per cent. In April 1933 Doctor Gibbons issued the following report: "The Romberg sign is negative and the patient feels remarkably well." In June 1933 there were 5,200,000 red cells and 81 per cent hemoglobin. In September 1933 Doctor Gibbons stated: "The Romberg sign is negative; coor-

dination is normal; the inferior tendon reflexes are hyperactive, the Babinski sign is negative, and vibratory sensation is normal." The red blood cells numbered 5,200,000, and the hemoglobin content was 95 per cent.

CASE 4 (Observed for Four Years).—A physician from another state, aged 60, consulted one of us in April 1931. He complained of bodily and mental fatigue, diminished manual dexterity and coordination in his surgical work and a mental feeling of indecision, which resulted in his temporarily discontinuing his professional work. His blood picture was of pernicious type and showed 3,500,000 red cells and 65 per cent hemoglobin. Repeated analyses of the gastric contents revealed an absence of free hydrochloric acid. Examination showed diminution of knee jerks and absence of ankle jerks, dorsiflexion responses of the great toes, diminution of vibratory sensation at the ankles, particularly over the left ankle. There was a slight Romberg sign and ataxia of all the extremities. In September 1931 the patient wrote: "A mental haze and confusion which had been present for a number of years disappeared, and there has been a marked recession in the numbness and stiffness of my fingers and feet. I am using desiccated stomach (ventriculin) at the present time, with apparently good results. My last blood count after a month of maintenance dose showed 5,600,000 red cells and 97 per cent hemoglobin." In April 1935 he wrote that an examination of the blood showed a red cell count of 4,900,000 and 83 per cent hemoglobin, that his general condition had been good in the interval, that he was much stronger physically and was better coordinated and that there was no evidence of material advance in the neural spinal involvement. The inferior tendon reflexes were unchanged, except that the left ankle jerk had returned; the Romberg sign was negative, and the plantar reflex was in flexion. Vibratory sensation was described as "unsatisfactory as to legs, apparently lost." This patient was first given liver extract;[17] later desiccated stomach, U. S. P., was used, and at the time of writing he states that intramuscular injections are much more efficient than oral ingestion of liver. This patient showed improvement in the following neurologic signs: return of one ankle jerk, a negative Romberg sign, better coordination, and reversal of the Babinski sign. From the analysis of signs, according to Grinker, further loss of vibration is questionable because of return of deep reflexes in the absence of signs referable to the pyramidal tract.

CASE 5 (Observed for Eight Years).—In 1926 a physician, aged 50, was examined by Dr. Alfred C. Reed and Dr. Joseph Catton of San Francisco because of gastro-intestinal disturbances which had existed for five years—the disorder being described by Doctor Reed as "spruelike" symptoms—and also because of dysesthesias, hypesthesias in all extremities, insecurity of balance and awkwardness of finger movements, which started later with the oncoming of anemia. Physical examination showed a moderate enlargement of the spleen, irregular, low grade fever and a low grade chronic ethmoid infection. The results of laboratory examinations were as follows: Eight or nine specimens of stool showed no parasites, abnormal constituents or excess of fat. The gastric analysis demonstrated absence of free hydrochloric acid. The blood showed 2,600,000 red cells, 60 per cent hemoglobin (Sahli), a color index of 1.15 and 4,725 white cells, with 56 per cent polymorphonuclears and 44 per cent lymphocytes. Study of a slide showed moderate poikilocytosis, no nucleated red cells and occasional large red cells which showed a slight amount of diffuse blueing. No punctate polychromatophilia was seen. Anisocytosis was rather marked. Most of the small cells were otherwise normal. The neutrophilic polymorphonuclear cells showed more than the usual polymorphism in the nucleus. Some had as many as seven distinct lobules. The

differential leukocyte count on the slide studied showed: polymorphonuclear neutrophils, 45 per cent; lymphocytes, 36 per cent; mononuclear and transitional cells, 10 per cent; eosinophilic polymorphonuclears, 7 per cent, and basophilic polymorphonuclears, 2 per cent. Neurologic examination showed diminution of superficial sensation in the great toe, fingers and lateral aspect of the left ankle, where vibratory sensation was also affected. The tendon reflexes were normal, save for hyperactive patellar reflexes. No pathologic signs referable to the pyramidal tract were elicited. The Romberg sign was slightly positive. Doctor Catton was inclined to ascribe the origin of the patient's symptoms to the cord rather than to the peripheral nerves. Doctor Reed believed that the picture was one of sprue rather than of pernicious anemia, despite definite pernicious features in the blood. The diet outlined included a high protein content with liver. The patient, who lives in another city, has been infrequently seen by us but has carefully observed his condition himself and controlled his treatment. In April 1935 he wrote: "At present there is slight remnant of paresthesia in the toes and fingers. The spot on the inner aspect of the left ankle is improved but still shows impaired sensation. Recovery of sensation in the toes and fingers is practically complete. The tendon reflexes are much less active and practically normal. Coordination of balance and finger movements is recovered almost completely, being 99 per cent plus. I have depended for the most part on fresh liver, lightly cooked, either fried or broiled, and I have been eating liver in that form for eight years. The daily average intake is from ⅓ to ½ pound (152 to 227 Gm.). Part of the time I have taken liver extract [17] to supplement, or in addition to, the fresh liver. I have not used the hypodermic form of liver extract for myself. I have also drunk from a pint to a quart (470 to 950 cc.) of acidophilus milk daily. I have taken buttermilk but no hydrochloric acid since I started the liver diet. I usually have liver for breakfast and also have meat for dinner. I use a few vegetables but no dessert or concentrated carbohydrates. I take cream, butter and meat fats freely. My diet is high in fats and proteins in relation to carbohydrates. My red cell count has averaged 6,000,000 or more over a period of several years, but the blood counts have been few and far between."

The characteristic neurologic symptoms, achlorhydria and blood picture would in our opinion fairly classify this case as one of pernicious anemia with neurologic complications, this diagnosis being confirmed by the course and favorable response to liver therapy.

Group 2.—This group comprises 3 cases.

Case 6 (Observed for Seven Years).—A woman, aged 70, an artist, was first seen in June 1928; she complained of unsteady gait, dysesthesias and a sore tongue. Examination revealed an atrophic glossitis, an ataxic gait, a suspicious extensor response of the left great toe, a positive Romberg sign and near absence of vibratory sensation in the lower extremities. The state of the inferior tendon reflexes was not noted. The blood showed a macrocytic anemia; the red cells numbered 3,200,000, and the hemoglobin content was 70 per cent. Ingestion of ½ pound (227 Gm.) of liver daily resulted in marked improvement; the soreness of the tongue disappeared, and the dysesthesias and unsteadiness became much less marked. In 1929 because of her improvement the patient discontinued taking liver, and her symptoms became aggravated. When the ingestion of liver was resumed, the symptoms subsided. In February, 1935, at the age of 77 years, the patient was remarkably active and felt quite well, except that she had slight dysesthesias and a feeling of unsteadiness and stiffness of her knees, which was not perceptible in her gait. The blood count showed 4,400,000 red cells and 88 per cent hemoglobin.

There was a slight Romberg sign; vibratory sensation was absent in the lower extremities; there was a questionable Babinski sign on the right; the patellar reflexes were sluggish, and the ankle reflexes were absent. During this entire period the patient had been able to continue her professional activities of painting in water colors.

CASE 7 (Observed for Seven and a Half Years).—A woman, aged 52, was first observed in the fall of 1927, complaining of dysesthesias in the extremities of one year's duration. She presented a typical picture of combined system disease of the cord and glossitis and a blood picture of macrocytic anemia, with 2,000,000 red cells and 46 per cent hemoglobin. She was given liver orally; in two months this treatment resulted in a rise of the number of red blood cells to 4,700,000, and of the hemoglobin content to 90 per cent; this was associated with remarkable betterment in her general physical and neurologic condition, the dysesthesia and ataxia becoming less marked. In April 1928 the pathologic signs referable to the pyramidal tract were lost. The blood counts, which attained a maximum of 4,900,000 in 1929, have been maintained at over 4,000,000 in subsequent years (on May 7, 1935, there were 4,750,000 red cells and 74 per cent hemoglobin); there has been a practically stationary condition in the patient's neurologic status; her weight has been maintained; she has experienced a feeling of well-being; there has been no return of glossitis, and gait and ability to walk and coordination have remained practically the same. This patient, therefore, has had a fairly satisfactory course for over seven years as a result of continuous liver therapy not precisely controlled, as the patient, who lives in a nearby town, comes to the office infrequently and must be urged to maintain her treatment because of her good performance and feeling of good health.

CASE 8 (Observed for Three Years).—A woman, aged 57, came to the clinic in September 1931, complaining of dysesthesias. Examination showed diminution of vibratory sensation, a positive Romberg sign, hyperactivity of the knee jerks, absence of ankle jerks, and a questionable Babinski sign. The red blood cells numbered 2,400,000 and the hemoglobin content was 59 per cent. The blood picture was that of macrocytic anemia. There was no free hydrochloric acid in the gastric contents. The patient was given liver extract [17] by mouth in large doses, and on Feb. 29, 1932, her red blood cells numbered 4,900,000 and the hemoglobin content was 97 per cent. She was then given 5 cc. of a solution of liver extract [17] intramuscularly each week; this therapy was continued until the patient was last seen, on Nov. 5, 1934, when her red cell count was 4,700,000 and the hemoglobin content was 93 per cent. Although dysesthesias were still present, her knee jerks were of normal intensity and her plantar reflex was in flexion. Otherwise the neurologic status was as before she received treatment.

COMMENT

The foregoing report of cases gives fair evidence of the specific action of liver on the neural manifestations of pernicious anemia in controlled, sustained adequate therapy. Cases are detailed in which the erythrocyte count was maintained at 5,000,000 for a year or more. Reference is particularly directed to case 1 (group 1), in which progression occurred during inadequate oral treatment consisting of what is ordinarily considered as maintenance dosage, yet in which marked improvement occurred after adequate parenteral therapy. The continued favorable response in this case (over three years) to parenteral

therapy suggests the effect of treatment to be one of replacement therapy rather than of temporary effectiveness. In case 3 (group 1) the clinical diagnosis of combined sclerosis after treatment could not be made from the clinical findings alone.

In contrast to the adverse reports of others, it is worthy of emphasis that in certain of these reports parenteral therapy was used in only a small number of cases and that the erythrocyte counts, as a rule, were below a figure reasonably to be designated as normal. The interpretation of neurologic signs on which Grinker and Kandel have laid so much emphasis in several of their cases may be influenced by several considerations: the variability of individual response from one examination to another, the probability of peripheral myelinic degeneration and, the most important consideration of all, whether abeyance of function in a neuron is always due to structural alteration or may be due to a reversible functional impairment. Our experience in cases of acute poliomyelitis is in favor of the latter contention. It is freely admitted that a structurally impaired central neuron is incapable of regeneration and that in such cases the degenerative process is merely arrested.

Another important consideration is the individual response to oral therapy and parenteral therapy. Whereas one patient may attain a satisfactory result from oral administration of liver, another may respond satisfactorily only to parenteral administration. Here again one may draw an analogy with syphilis.

Definite conclusions based on results of therapy at a time when liver therapy was at an early stage of development are scarcely applicable at present and may be compared with the earliest and unsatisfactory experience with digitalis therapy. It would be unfortunate, in our opinion, should the idea gain ground that the neural changes in pernicious anemia are due to something other than the deficiency causing the general picture of pernicious anemia and that, despite treatment, physicians may give their patients no assurance that their neurologic signs will not progress. Although the number of adequately treated patients is small, the results have an added signification in that there is no record in the series of progression in adequately treated patients.

CONCLUSIONS

Reports are submitted of the results of sustained, adequate and controlled treatment of patients with neurologic complications of pernicious anemia.

Adequate treatment as defined and illustrated is efficacious in both arresting and improving neurologic complications of pernicious anemia.

EXPERIMENTAL RENAL INSUFFICIENCY PRODUCED BY PARTIAL NEPHRECTOMY

V. DIETS CONTAINING WHOLE DRIED MEAT

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In previous reports [1] it was shown that partial nephrectomy is followed by a progressive development of polyuria, albuminuria, nitrogen retention, renal hypertrophy, hypertension and cardiac hypertrophy. Feeding different concentrations of whole dried liver produced variations in this syndrome and in the pathologic changes in the kidney. The present report is concerned with the effect of whole meat on the partially nephrectomized rat. It demonstrates that whole dried meat causes changes in the syndrome similar to those produced by diets containing liver.

EXPERIMENTAL METHODS

Details of the experimental procedures have been presented in previous papers.[1] In these as in former experiments the control animals included rats with both kidneys intact and unilaterally nephrectomized rats. The partially nephrectomized animals were those in which from 80 to 90 per cent of the total renal tissue was removed by a two stage operation.

Two procedures were used in the determination of renal function. The first was a determination of the volume, specific gravity and protein of the urine after the animal was without food and water for twenty-four hours. This will be called the concentration test. Second, a week later, a modified Addis urea clearance test was carried out as follows: Food was withdrawn for sixteen hours; the animal was then given a 5 per cent solution of urea by stomach tube, the number of cubic centimeters being equal to one fortieth of the number of square centimeters of surface area. The voided urine was collected for six hours, and residual urine was obtained by massaging the abdominal wall; blood was obtained by clip-

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From the Laboratory of Physiological Chemistry, the University of Virginia.

The pathologic study was made by Dr. Paul Kimmelstiel of the Department of Pathology, the Medical College of Virginia.

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1. (*a*) Chanutin, Alfred, and Ferris, E. B., Jr.: Experimental Renal Insufficiency Produced by Partial Nephrectomy: I. Control Diet, Arch. Int. Med. **49**: 767 (May) 1932. (*b*) Chanutin, Alfred: Experimental Renal Insufficiency Produced by Partial Nephrectomy: III. Diets Containing Whole Dried Liver, Liver Residue and Liver Extract, ibid. **54**:720 (Nov.) 1934.

ping the tail at the middle of this six hour period. The funnel of the metabolism cage was not washed, since it was assumed that only a negligible amount of urine dried on the surface. The urine and blood were not analyzed in the presence of diarrhea. The amount of urea in the blood and urine was determined by the gasometric urease method of Van Slyke.[2] The urea ratio was calculated from the formula $\frac{\text{urea excretion per hour}}{\text{urea in 100 cc. of blood}}$. The specific gravity of the urine was corrected for the amount of albumin by applying the equation of Lashmet and Newburgh;[3] specific gravity correction = 0.003 × percentage of protein. The correction was applied to the values for specific gravities with the realization that the factor was intended for urine from human subjects. No corrections were made for urinary volumes under 4 cc., since the excretion of protein was not estimated in these cases.

From about five to seven days after the determination of the urea ratio, the animal was killed. Blood pressure readings were obtained by inserting a needle into the carotid artery while the animal was under ether anesthesia. The heart and kidneys were weighed immediately after removal, having been dried of superficial blood and urine on filter paper. No attempt was made to differentiate the effect of sex on the weight of the kidneys. The surface area was calculated

TABLE 1.—*Composition of Rations*

Diet	Concentration of Component in Diet, Percentage						
	Dried Whole Meat	Starch	Lard	Cod Liver Oil	Dried Yeast	Salt Mixture	Nitrogen
M 10	10	62	14	5	5	4	1.7
M 20	20	52	14	5	5	4	2.8
M 40	40	32	14	5	5	4	5.2
M 80	80	..	6	5	5	4	10.6

from the weight of the animal by the formula of Lee.[4] The ratio of the weight of the heart and kidneys to the surface area is expressed by $\frac{\text{H.W.}}{\text{S.A.}}$ and $\frac{\text{K.W.}}{\text{S.A.}}$ respectively.

Four experimental diets were used and were designated as M 10, M 20, M 40 and M 80, in accordance with the percentage of whole dried meat which they contained. The composition of the diets is shown in table 1. The diets differed chiefly in the percental concentration of whole dried meat, which was the chief source of protein. A large quantity of cold storage lean meat was ground without loss of tissue juice, dried in a large steam-heated container and ground to a fine powder.

For histologic study, the kidneys were fixed in a dilute solution of formaldehyde U. S. P. (1:10), embedded in paraffin and stained with hematoxylin and eosin. The pathologic findings were classified independently by Dr. Paul Kimmelstiel, of the department of pathology of the Medical College of Virginia, on the following basis:

The changes in the tubules are graded from 1 to 4 solely on the basis of dilatation. Grade 1 represents the slightest degree of recognizable dilatation, and grade 4 indicates the most marked. Changes in the epithelium of the tubules, such as

2. Van Slyke, D. D.: J. Biol. Chem. **73**:695, 1927.

3. Lashmet, F. H., and Newburgh, L. H.: Specific Gravity of Urine as a Test of Kidney Function, J. A. M. A. **94**:1883 (June 14) 1930.

4. Lee, M. O.: Am. J. Physiol. **89**:24, 1929.

granules and vacuoles or enlargement and sloughing of cells, could not be expressed in numerical gradation, but in general these evidences of degeneration increased with the dilatation of the tubules.

The earliest glomerular change is apparently manifested by swelling of the epithelial cells, which is followed by thickening and hyalinization of the connective tissue framework. In the most advanced stages, these pictures are complicated by adhesions of the glomeruli associated with proliferation of the parietal cells of Bowman's capsule and necrosis of the capillary loops. These changes are of focal distribution. In grading the glomerular damage, the numerals from 1 to 4 give a general impression of the relative severity of these focal degenerative and inflammatory changes.

EXPERIMENTAL RESULTS AND ANALYSIS OF OBSERVATIONS

Controls.—A summary of results, including blood pressure, $\frac{\text{H. W}}{\text{S. A.}}$ and $\frac{\text{K. W.}}{\text{S. A.}}$ ratios, response to the concentration test and urea ratio, for one hundred and fifty-one rats which were intact or unilaterally nephrectomized is presented in table 2. The $\frac{\text{K. W.}}{\text{S. A.}}$ ratios and the urea ratio are supplemented by additional values for a special group of control animals.

Of the seventy-three intact animals, there was but one with an elevated blood pressure (150 mm.). There were four with blood pressures above 140 mm. among the seventy-eight unilaterally nephrectomized animals. The mean values for blood pressure in the two groups on each diet were so close together that both groups were used in calculating the standard error for each diet. It can be seen that the various diets caused no significant changes in the blood pressure. The mean values for the $\frac{\text{H. W.}}{\text{S. A.}}$ ratio in the different dietary groups are remarkably constant, and the standard errors are very small. There is therefore a constant relationship between this ratio and the blood pressure in control animals.

There is a progressive increase in the $\frac{\text{K. W.}}{\text{S. A.}}$ ratio with the increased protein intake (chart 1). If the average $\frac{\text{K. W.}}{\text{S. A.}}$ ratio for the intact M 10 animals is considered as 1, the intact animals on the M 20, M 40 and M 80 diets show comparative ratios of 1.10, 1.19 and 1.33, respectively: if the ratio for the unilaterally nephrectomized animals on the M 10 diet is considered as 1, the increases were 1.06, 1.19 and 1.44, respectively. These results indicate that the most marked hypertrophy was obtained in the unilaterally nephrectomized rats on the M 80 diet.

If a comparison of the $\frac{\text{average kidney weight of unilaterally nephrectomized rats}}{\text{average kidney weight of intact rats}}$ ratios is made, values of 0.69, 0.67, 0.69 and 0.75 are obtained for the animals on the M 10, M 20, M 40 and M 80 diets, respectively. If renal hypertrophy is due to the increased excretory load, it would be assumed that these ratios would become progressively greater as the amount of protein ingested increased, since the single kidney must do

TABLE 2.—*Observations on Control Animals Fed a Variety of Diets*

Rats	Renal Condition and Diet	Value	Weight, Gm.	Duration of Experiment, Days	Blood Pressure, Mm.	Heart Weight / Surface Area × 100	Kidney Weight / Surface Area × 100†	Twenty-Four Hour Urine Concentration Test: Volume, Cc.	Twenty-Four Hour Urine Concentration Test: Specific Gravity	Urine Urea per Hour: Urea in 100 Cc. Blood
15	2 kidneys M 10	Minimum	178	14	106	0.159	0.342	1.0	1.0297	28
		Maximum	320	203	150	0.189	0.495 (30)	4.6	1.0547	70 (40)
		Average			123	0.175	0.401 ± 0.008	2.6	1.0433	50 ± 1.93
16	1 kidney M 10	Minimum	130	14	106	0.141	0.240	0.7	1.0291	23
		Maximum	354	248	158	0.212	0.378 (27)	3.9	1.0575	52 (43)
		Average			124	0.172	0.277 ± 0.008	2.1	1.0433	35 ± 1.11
					*124 ± 2.76	*0.173 ± 0.003				
21	2 kidneys M 20	Minimum	194	34	106	0.141	0.350	0.7	1.0355	35
		Maximum	432	207	134	0.207	0.550 (31)	4.5	1.0676	80 (42)
		Average			122	0.182	0.440 ± 0.008	2.7	1.0499	60 ± 2.16
22	1 kidney M 20	Minimum	178	55	106	0.157	0.252	0.5	1.0351	29
		Maximum	330	286	138	0.204	0.332 (33)	4.4	1.0481	59 (44)
		Average			121	0.172	0.293 ± 0.005	2.9	1.0493	42 ± 1.35
					*121 ± 1.20	*0.177 ± 0.002				
17	2 kidneys M 40	Minimum	188	29	108	0.155	0.350	1.7	1.0300	30
		Maximum	416	225	132	0.204	0.623 (28)	5.5	1.0679	82 (34)
		Average			120	0.177	0.477 ± 0.011	3.1	1.0513	62 ± 2.11
19	1 kidney M 40	Minimum	184	66	108	0.148	0.294	1.2	1.0276	28
		Maximum	444	219	146	0.232	0.378 (30)	6.7	1.0689	55 (36)
		Average			124	0.173	0.330 ± 0.007	3.1	1.0511	42 ± 1.50
					*122 ± 1.45	*0.177 ± 0.004				
20	2 kidneys M 80	Minimum	206	29	104	0.142	0.485	2.3	1.0357	47
		Maximum	344	203	138	0.206	0.648 (34)	4.0	1.0641	103 (33)
		Average			122	0.170	0.533 ± 0.010	2.6	1.0516	66 ± 2.90
21	1 kidney M 80	Minimum	176	45	96	0.143	0.328	0.4	1.0390	23
		Maximum	414	203	150	0.193	0.474 (33)	4.8	1.0809	66 (58)
		Average			124	0.167	0.399 ± 0.009	2.6	1.0555	41 ± 1.58
					*123 ± 1.87	*0.170 ± 0.054				

* Average and standard error for control animals on a specific diet.

† The $\frac{K.W.}{S.A.}$ ratio and the urea ratio are represented by a larger number of animals which are indicated by the figures in parenthesis.

twice its normal work. The results obtained were unusually uniform, with the possible exception of those obtained in the group receiving the M 80 diet.

The volume of urine excreted during the concentration test was 5 cc. in only two cases and was between 4 and 5 cc. in eight cases. The vast majority of the volumes were found to be between 1 and 3 cc.

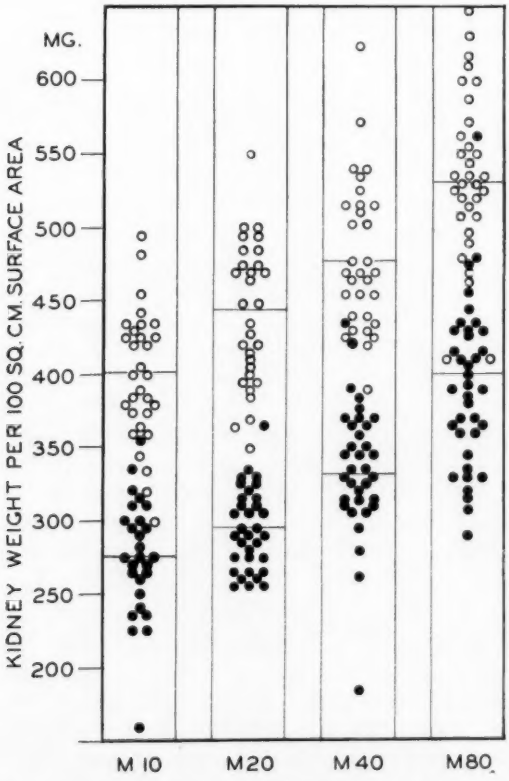

Chart 1.—The effect of diet on the $\frac{K.W.}{S.A.}$ ratio in intact and in unilaterally nephrectomized rats. The unshaded circles indicate the animals with two kidneys; the shaded circles indicate those with one kidney.

The average values for volume are uniform in the eight groups, and there seems to be no significant effect of diet on the volume of urine obtained during the concentration test. Although there was a great individual variation in the specific gravity, the averages for each group appear to be representative; the urine from animals on the diet con-

TABLE 3.—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 10 Per Cent of Whole Meat*

Rat	Duration of Experiment, Days	Surface Area, Sq. Cm.	Blood Pressure, Mm.	Heart Weight / Surface Area × 100	Kidney Weight / Surface Area × 100	Twenty-Four Hour Urine Concentration Test: Volume, Cc.	Specific Gravity	Albumin, Gm.	Urea Ratio	Pathologic Change: Tubule	Pathologic Change: Glomerulus
1	14	234	122	0.137	0.089	8.0	1.0199	.....	..	..	..
2	14	237	152	0.136	0.110	6.5	1.0222	0.008	..	..	..
3	43	279	122	0.197	0.146	6.0	1.0226	0.004	..	..	..
4	53	292	128	0.159	0.133	8.2	1.0255	0.005	..	..	..
5	53	235	112	0.175	0.155	4.4	1.0204	0.003	..	..	..
6	57	248	142	0.198	0.145	5.9	1.0260	.....	..	1	0
7	60	283	130	0.165	0.169	4.3	1.0281	.....	..	..	..
8	60	222	126	0.149	0.101	3.6	1.0280	.....	..	..	..
9	61	222	110	0.169	0.117	3.7	1.0236	.....	..	..	..
10	61	224	104	0.137	0.131	3.4	1.0272	.....	..	..	..
11	61	271	130	0.164	0.132	3.3	1.0332	.....	..	..	..
12	101	282	122	0.196	0.179	3.5	1.0328	.....	15	..	..
13	101	257	168	0.231	0.127	8.8	1.0174	0.058	..	..	..
14	101	326	138	0.209	0.163	4.5	1.0318	0.016	16	..	..
15	101	274	118	0.200	0.146	4.7	1.0254	.....	..	..	..
16	128	286	130	0.186	0.177	3.6	1.0335	0.012	16	..	..
17	135	339	140	0.202	0.214	8.6	1.0214	.....	..	1	0
18	138	302	144	0.184	0.167	5.2	1.0248	0.040	..	1	0
19	138	295	126	0.192	0.181	4.2	1.0220	0.018	..	1	0
20	142	275	126	0.184	0.240	3.6	1.0379	0.028	22	..	..
21	142	248	132	0.177	0.170	3.5	1.0343	0.001	17	..	..
22	142	232	126	0.213	0.186	4.9	1.0271	0.001	16	..	..
23	142	270	126	0.166	0.207	4.1	1.0310	0.002	21	..	..
24	142	284	126	0.168	0.169	3.6	1.0376	.....	18	..	..
25	142	299	148	0.178	0.176	2.2	1.0468	.....	21	..	..
26	142	228	146	0.170	0.160	3.3	1.0249	.....	11	..	..
27	142	266	132	0.176	0.169	2.9	1.0379	.....	19	..	..
28	142	275	136	0.177	0.204	2.0	1.0406	.....	22	..	..
29	146	341	154	0.172	0.187	6.1	1.0247	0.062	14	..	..
30	146	304	114	0.192	0.159	4.5	1.0240	.....	12	..	..
31	146	336	114	0.176	0.161	3.6	1.0236	.....	11	..	..
32	146	260	162	0.169	0.144	10.2	1.0167	0.072	9	..	..
33	146	263	164	0.183	0.152	6.8	1.0167	0.024	..	..	..
34	147	320	144	0.194	0.215	2.8	1.0289	.....	16	..	..
35	147	254	142	0.171	0.171	3.6	1.0317	.....	9	..	..
36	147	258	126	0.182	0.142	3.2	1.0319	.....	10	..	..
37	152	328	208	0.250	0.189	9.2	1.0171	0.021	..	..	..
38	152	191	132	0.168	0.155	1.8	1.0257	.....	..	..	..
39	152	202	188	0.233	0.201	1.8	1.0326	.....	9	..	..
40	155	262	192	0.226	0.200	9.2	1.0140	0.038	12	..	..
41	155	334	154	0.185	0.183	4.0	1.0312	.....	24	..	..
42	155	346	148	0.185	0.179	4.1	1.0297	.....	15	..	..
43	159	266	150	0.184	0.217	4.5	1.0267	0.009	..	0	0
44	159	273	152	0.183	0.226	2.9	1.0281	.....	..	1	0
45	168	322	124	0.183	0.186	5.4	1.0288	0.005	16	1	0
46	168	320	152	0.208	0.235	4.6	1.0273	0.059	15	2	1
47	168	336	148	0.180	0.170	3.8	1.0291	.....	13	1	0
48	168	318	130	0.160	0.167	2.6	1.0308	.....	12	..	..
49	168	283	134	0.169	0.153	5.3	1.0267	0.011	14	1	1
50	179	330	142	0.186	0.197	4.1	1.0290	.....	16	..	..
51	179	358	136	0.186	0.272	4.8	1.0312	0.080	39	..	..
52	179	318	154	0.202	0.202	5.2	1.0173	0.018	20	..	..
53	206	250	186	0.212	0.270	...	.....	.....	..	1	1
54	213	322	168	0.216	0.202	...	.....	.....	..	..	..
55	213	315	150	0.216	0.175	...	.....	.....	..	2	1
56	226	345	138	0.200	0.204	3.3	1.0290	.....	21	..	..
57	226	216	178	0.248	0.287	6.7	1.0160	0.002	7	..	..
58	226	378	154	0.212	0.220	3.8	1.0295	.....	4	..	..
59	232	326	142	0.284	0.252	...	.....	.....	..	..	..
60	238	299	118	0.194	0.154	2.5	1.0465	.....	..	1	1
61	238	320	150	0.244	0.219	3.0	1.0498	.....	..	2	II
62	238	304	138	0.183	0.200	3.0	1.0483	.....	..	1	1
63	246	282	134	0.162	0.149	...	.....	.....	..	1	0
64	251	272	150	0.176	0.167	...	.....	.....	..	0	0
65	251	268	128	0.161	0.134	...	.....	.....	..	0	0
66	263	346	126	0.230	0.189	6.3	1.0300	0.061	..	1	0
67	263	310	130	0.202	0.213	3.7	1.0372	.....	..	1	0

taining the lowest amount of meat showed the lowest specific gravity (1.0433), and that from the animals on the diet containing the highest amount of meat showed the highest average value (1.0555). The value for urinary protein, determined in five animals, was found to be 0.010, 0.020, 0.024, 0.042 and 0.047 Gm., respectively.

The individual values for the urea ratio, $\frac{\text{urea excreted in one hour's urine}}{\text{urea in 100 cc. of blood}} \times 100$, varied appreciably in the control animals on various diets. The average values for the ratio in animals with both kidneys intact were

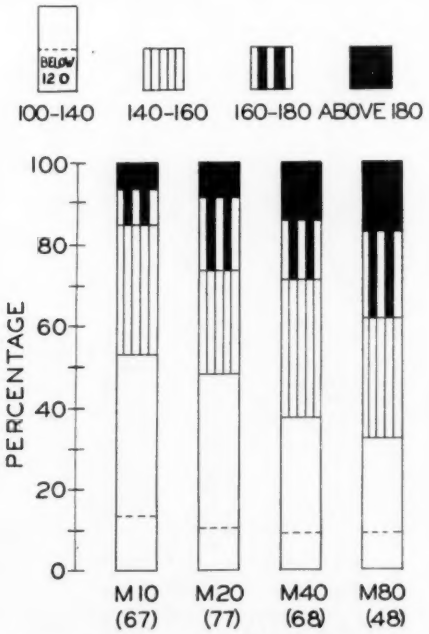

Chart 2.—The effect of diet on the blood pressure of partially nephrectomized rats.

50, 60, 62 and 66 for the groups receiving the M 10, M 20, M 40 and M 80 diets, respectively, whereas the ratios for the unilaterally nephrectomized animals on the same diets were 35, 42, 42 and 41. This shows that the ability to excrete urea increases markedly in the intact animals fed the diets containing a higher percentage of protein but is relatively constant in the animals with one kidney. A comparison of the $\frac{\text{average urea ratio of unilaterally nephrectomized rats}}{\text{average urea ratio of intact rats}}$ ratios gives values of 0.70, 0.70, 0.68 and 0.62. This indicates decreased renal function in the unilaterally nephrectomized animals as the protein content of the diet

TABLE 4.—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 20 Per Cent of Whole Meat*

Rat	Duration of Experiment, Days	Surface Area, Sq. Cm.	Blood Pressure, Mm.	Heart Weight: Surface Area × 100	Kidney Weight: Surface Area × 100	Twenty-Four Hour Urine Concentration Test: Volume, Cc.	Specific Gravity	Albumin, Gm.	Urea Ratio	Pathologic Change: Tubule	Pathologic Change: Glomerulus
1	14	221	126	0.164	0.119	7.8	1.0199	0.003	..	..	..
2	14	248	144	0.148	0.125	7.4	1.0254	0.009	..	..	..
3	14	231	162	0.159	0.134	...	.....	.....	..	..	..
4	14	283	114	0.170	0.148	5.2	1.0310	0.009	..	..	..
5	55	255	162	0.232	0.180	9.8	1.0235	0.240	..	1	0
6	55	248	130	0.148	0.118	7.6	1.0190	0.025	..	1	0
7	55	293	164	0.173	0.174	5.9	1.0260	0.014	..	..	..
8	57	304	122	0.179	0.212	2.6	1.0370	.....	..	1	0
9	57	252	104	0.154	0.161	3.0	1.0308	.....	..	0	0
10	57	307	126	0.193	0.142	6.2	1.0207	0.031	..	..	..
11	57	306	126	0.175	0.150	10.6	1.0212	0.037	..	0	1
12	57	294	128	0.184	0.206	8.6	1.0222	0.100	..	1	1
13	57	314	172	0.249	0.191	8.0	1.0206	0.069	..	2	1
14	57	364	142	0.205	0.198	4.9	1.0367	0.043	..	..	..
15	57	294	132	0.179	0.188	4.0	1.0333	0.005	..	0	0
16	57	283	172	0.210	0.168	6.3	1.0278	0.045	..	2	1
17	61	322	136	0.187	0.178	8.8	1.0273	0.051	..	..	..
18	61	301	118	0.174	0.140	7.6	1.0286	0.027	..	..	..
19	62	339	132	0.195	0.205	6.3	1.0200	0.029	..	..	..
20	62	339	94	0.204	0.208	7.5	1.0247	0.014	..	..	..
21	87	329	190	0.244	0.213	8.6	1.0222	0.088	7	..	..
22	90	368	118	0.178	0.217	6.2	1.0320	.....	15	..	..
23	90	341	154	0.197	0.249	11.3	1.0198	.....	9	1	1
24	90	307	120	0.171	0.200	6.7	1.0244	.....	23	..	..
25	90	286	130	0.164	0.206	5.8	1.0262	.....	13	..	..
26	105	389	152	0.214	0.214	6.6	1.0270	0.069	9	..	..
27	107	362	...	.....	.....	7.0	1.0284	0.068	8	..	..
28	114	228	222	0.210	0.193	11.6	1.0155	0.045	7	..	..
29	120	324	138	0.166	0.216	6.8	1.0241	0.056	..	..	..
30	120	324	204	0.214	0.306	11.0	1.0229	0.168	11	..	..
31	122	386	118	.....	.....	4.0	1.0397	.....	..	..	..
32	130	372	122	0.178	0.208	7.2	1.0229	0.027	12	..	..
33	130	390	132	0.173	0.290	10.0	1.0229	0.124	12	..	..
34	130	386	118	0.157	0.230	3.9	1.0321	.....	26	..	..
35	130	356	126	.....	0.248	10.3	1.0173	0.661	13	..	..
36	134	328	162	0.184	0.228	7.1	1.0230	0.053	16	..	..
37	134	336	130	0.182	0.205	7.1	1.0242	0.068	17	..	..
38	138	333	132	0.208	0.216	12.5	1.0168	.....	..	1	1
39	138	364	132	0.209	0.205	6.0	1.0271	0.042	..	1	1
40	140	280	126	0.164	0.227	3.1	1.0407	.....	23	..	..
41	140	392	138	0.194	0.276	5.6	1.0345	0.129	29	..	..
42	141	280	150	0.194	0.207	5.3	1.0198	0.041	..	1	1
43	141	270	116	0.188	0.192	3.4	1.0297	.....	..	..	..
44	141	270	176	0.188	0.294	11.3	1.0207	0.196	..	2	III
45	141	370	150	0.229	0.254	6.0	1.0157	0.045	..	..	..
46	146	370	148	0.161	0.242	10.4	1.0204	0.050	6	..	..
47	146	278	174	0.175	0.216	9.0	1.0181	0.061	5	..	..
48	153	358	158	0.212	0.299	10.6	1.0180	0.078	..	..	..
49	153	262	220	0.241	0.250	7.3	1.0165	0.001	4	..	..
50	154	306	156	0.248	0.344	10.7	1.0215	0.176	7	..	..
51	166	313	134	0.188	0.310	9.0	1.0209	0.097	16	..	..
52	166	345	122	0.176	0.222	11.9	1.0178	0.069	11	..	..
53	166	370	164	0.214	0.270	11.6	1.0191	0.050	8	..	..
54	166	427	148	0.207	0.266	21.5	1.0178	0.300	14	..	..
55	166	323	142	0.168	0.222	4.0	1.0365	.....	27	..	..
56	166	374	112	0.184	0.224	5.5	1.0311	0.037	20	..	..
57	166	326	144	0.198	0.231	4.2	1.0391	.....	24	..	..
58	166	307	124	0.179	0.209	5.1	1.0331	0.027	20	..	..
59	166	272	164	0.237	0.284	8.0	1.0181	0.068	5	..	..
60	166	245	170	0.239	0.176	...	.....	.....	..	3	IV
61	171	306	204	0.257	0.210	9.5	1.0145	.....	..	3	IV
62	171	395	128	0.179	0.240	2.8	1.0365	.....	..	1	0
63	178	328	158	0.183	0.252	5.6	1.0293	0.062	23	..	..
64	178	433	168	0.214	0.394	11.2	1.0241	0.137	..	..	..
65	183	383	138	0.214	0.309	10.5	1.0251	0.190	12	..	..
66	183	368	148	0.218	0.338	9.5	1.0253	0.175	..	..	..
67	183	354	132	0.196	0.266	7.8	1.0270	0.137	14	..	..
68	187	354	116	0.171	0.223	4.3	1.0333	.....	..	..	..
69	202	304	150	0.191	0.277	3.2	1.0322	.....	14	..	..
70	202	320	126	0.197	0.215	3.5	1.0469	.....	16	..	..
71	202	308	184	0.209	0.209	3.8	1.0296	.....	13	..	..
72	202	289	148	0.198	0.346	9.0	1.0282	0.152	7	..	..
73	202	400	144	0.212	0.490	10.3	1.0202	0.090	10	..	..
74	217	354	172	0.196	0.229	12.7	1.0156	0.088	1	..	..
75	217	354	156	0.188	0.273	15.0	1.0172	0.114	3	..	..
76	226	318	140	0.197	0.254	4.0	1.0350	.....	..	..	..
77	286	367	146	0.173	0.432	2.8	1.0245	.....	..	1	0

increases. These values are similar to those obtained in intact dogs [5] and rabbits [6] maintained on standard diets.

Because the values listed in table 2 were fairly constant in all control animals, the following values have been taken as the limits of normal for all the animals: blood pressure below 140 mm. of mercury, urinary volume below 5 cc., urinary specific gravity above 1.04, urinary protein content below 0.05 and urea ratio above 30.

Effect of Diet on Experimental Animals in Good Health.—The effects of the M 10, M 20, M 40 and M 80 diets on partially nephrectomized rats are shown in detail in tables 3 to 6, respectively. Charts 2 to 7 were prepared from these tables to facilitate comparisons of the effects of the different diets on the blood pressure, urinary volume, urinary specific gravity after correction was made for albumin, urinary protein, urea ratio and kidney weight, respectively.

Blood Pressure: The effects of diet on blood pressure are summarized in chart 2. There is a progressive decrease in the number of animals having blood pressures below 140 mm. as the concentration of meat in the diet increases. Conversely, the incidence of significant hypertension (over 160 mm.) is definitely increased with diets containing more meat. However, individual maximum values for blood pressure do not appear to be influenced by the diet. Because of the relatively small number of rats killed during the first few months after operation, it is impossible to draw conclusions concerning the time of appearance and the ultimate incidence of increased blood pressures.

The relationship between hypertension and the $\frac{\text{H. W.}}{\text{S. A.}}$ ratios varied with the different diets. In the younger animals the relationship was poor as a general rule. The correlation coefficients and their probable errors were calculated for the blood pressure and the $\frac{\text{H. W.}}{\text{S. A.}}$ ratio for each diet as follows: M 10, 0.43 ± 0.065 (substantial relationship); M 20, 0.61 ± 0.048 (very substantial relationship); M 40, 0.30 ± 0.075 (low relationship); M 80, 0.47 ± 0.076 (substantial relationship). The low correlation coefficient found in the animals which were fed the M 40 diet cannot be explained. These results, representing the partially nephrectomized animals only, do not show as high a degree of correlation as that obtained in previous reports [7] in which control animals were included.

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TABLE 5.—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 40 Per Cent of Whole Meat*

Rat	Duration of Experiment, Days	Surface Area, Sq. Cm.	Blood Pressure, Mm.	Heart Weight / Surface Area × 100	Kidney Weight / Surface Area × 100	Twenty-Four Hour Urine Concentration Test: Volume, Cc.	Specific Gravity	Albumin, Gm.	Urea Ratio	Pathologic Change: Tubule	Glomerulus
1	29	358	108	0.194	0.223	...	.....	.....	..	..	..
2	29	316	138	0.183	0.188	...	.....	.....	..	..	..
3	47	299	136	0.159	0.155	13.5	1.0150	.....	..	3	I
4	47	343	158	0.171	0.214	7.3	1.0270	.....	..	3	I
5	47	249	180	0.169	0.183	6.1	1.0189	.....	..	2	I
6	47	330	156	0.177	0.192	14.2	1.0174	.....	..	0	0
7	47	323	124	0.195	0.206	13.6	1.0194	.....	..	..	..
8	47	337	136	0.192	0.166	13.5	1.0185	.....	..	1	I
9	47	327	128	0.198	0.171	15.0	1.0177	.....	..	..	..
10	50	274	138	0.199	0.236	...	.....	.....	..	..	..
11	66	339	162	0.175	0.268	7.2	1.0276	.....	15	..	..
12	66	343	124	0.168	0.302	5.6	1.0443	0.009	24	..	..
13	66	234	134	0.224	0.343	2.8	1.0634	.....	20	..	..
14	66	265	136	0.149	0.204	4.1	1.0229	0.000	6	..	..
15	66	260	152	0.158	0.200	9.0	1.0174	.....	4	..	..
16	66	339	152	0.185	0.239	12.0	1.0169	0.088	3	..	..
17	66	252	144	0.161	0.266	3.1	1.0246	.....	13	..	..
18	66	318	126	0.168	0.253	4.9	1.0410	0.010	15	..	..
19	67	328	116	0.170	0.239	9.6	1.0273	0.040	13	..	..
20	67	276	146	0.174	0.248	5.7	1.0274	0.002	17	..	..
21	67	348	146	0.181	0.262	8.7	1.0312	0.017	13	..	..
22	67	270	116	0.158	0.218	7.2	1.0228	0.034	11	..	..
23	74	408	128	0.185	0.245	6.7	1.0302	0.096	16	..	..
24	74	355	198	0.190	0.407	9.1	1.0278	0.177	8	..	..
25	74	379	146	0.177	0.314	6.7	1.0285	.....	16	..	..
26	80	354	140	0.188	0.244	7.6	1.0271	0.080	..	..	..
27	80	370	148	0.192	0.197	12.0	1.0176	0.002	..	..	..
28	84	366	164	0.196	0.188	18.3	1.0162	0.122	3	..	..
29	84	336	182	0.204	0.241	17.6	1.0147	0.027	8	..	..
30	84	403	154	0.193	0.288	11.0	1.0215	0.093	4	..	..
31	86	249	170	0.212	0.187	....	.....	.....	..	..	..
32	87	238	168	0.246	0.216	....	.....	.....	..	..	..
33	96	295	134	0.177	0.286	11.0	1.0162	.....	..	..	..
34	118	373	138	0.196	0.302	13.3	1.0213	0.107	..	..	..
35	118	386	154	0.214	0.324	20.8	1.0156	0.196	..	..	..
36	118	390	148	0.207	0.408	11.8	1.0241	.....	..	3	II
37	118	340	208	0.300	0.258	20.5	1.0123	0.226	4	4	III
38	129	328	174	0.191	0.374	11.1	1.0190	0.117	..	3	IV
39	129	394	170	0.206	0.392	18.7	1.0158	0.168	2	..	..
40	134	416	128	0.201	0.328	....	.....	.....	14	2	I
41	134	297	148	0.184	0.233	....	.....	.....	12	..	..
42	134	372	144	0.188	0.298	....	.....	.....	8	4	II
43	134	314	126	0.169	0.339	11.4	1.0181	0.199	8	3	III
44	134	308	196	0.195	0.292	16.4	1.0150	0.164	7	..	..
45	134	302	150	0.230	0.305	15.3	1.0162	0.075	8	..	..
46	134	336	164	0.180	0.346	19.2	1.0148	0.144	..	..	..
47	134	336	152	0.184	0.274	16.2	1.0145	0.121	..	..	..
48	134	362	168	0.168	0.324	16.2	1.0177	0.183	..	2	III
49	134	343	128	0.160	0.346	8.7	1.0240	0.165	..	..	..
50	134	336	158	0.190	0.405	17.1	1.0137	0.104	..	..	..
51	134	355	144	0.166	0.467	9.5	1.0237	0.145	..	..	..
52	134	306	148	0.156	0.300	7.1	1.0253	0.122	..	..	..
53	141	308	166	0.195	0.302	13.0	1.0164	0.162	9	..	..
54	142	390	184	0.248	0.324	17.2	1.0147	0.098	6	4	III
55	155	413	172	0.211	0.398	14.3	1.0202	0.236	..	..	..
56	160	412	130	0.167	0.356	2.9	1.0565	.....	..	..	..
57	160	352	204	0.220	0.344	16.1	1.0171	0.262	..	..	..
58	160	323	122	0.192	0.280	7.5	1.0272	0.140	..	..	..
59	160	317	196	0.198	0.497	7.5	1.0247	0.157	..	..	..
60	160	343	152	0.186	0.355	9.5	1.0207	0.144	..	..	..
61	160	316	132	0.162	0.304	7.6	1.0180	0.110	9	..	..
62	160	390	124	0.178	0.329	11.5	1.0193	0.086	11	3	II
63	160	308	154	0.192	0.286	9.1	1.0150	0.061	8	3	II
64	171	408	210	0.238	0.339	...	.....	.....	..	..	..
65	179	458	150	0.230	0.437	11.8	1.0230	0.150	..	..	..
66	179	318	180	0.264	0.407	10.6	1.0254	0.087	..	..	..
67	225	314	146	0.240	0.364	18.3	1.0206	0.240	6	..	..
68	225	370	138	0.185	0.339	1.0	1.0395	.....	..	..	..

Urine Concentration Test: Chart 3 shows the effect of various diets on the urinary volume of partially nephrectomized animals. There is a progressive increase in the incidence and degree of polyuria with

TABLE 6.—*Observations on Partially Nephrectomized Animals Receiving a Diet Containing 80 Per Cent of Whole Meat*

Rat	Duration of Experiment, Days	Surface Area, Sq. Cm.	Blood Pressure, Mm.	Heart Weight: Surface Area × 100	Kidney Weight: Surface Area × 100	Twenty-Four Hour Urine Concentration Test: Volume, Cc.	Specific Gravity	Albumin, Gm.	Urea Ratio	Pathologic Change: Tubule	Glomerulus
1	29	249	134	0.160	0.280	...	.....	.....	..	..	..
2	29	254	112	0.179	0.264	...	.....	.....	..	..	..
3	29	290	140	0.196	0.278	...	.....	.....	..	..	..
4	29	283	142	0.212	0.338	...	.....	.....	..	..	..
5	45	294	116	0.165	0.292	10.0	1.0210	.....	..	..	..
6	45	248	120	0.151	0.292	11.7	1.0181	0.134	..	..	..
7	45	271	152	0.230	0.276	15.6	1.0176	0.234	..	..	..
8	45	262	148	0.191	0.264	9.0	1.0206	0.082	..	..	..
9	45	...	...	.....	.....	9.8	1.0206	.....	..	..	..
10	45	186	218	0.210	0.236	...	.....	.....	..	4	III
11	46	316	146	0.204	0.354	17.5	1.0200	0.247	..	..	..
12	64	260	142	0.139	0.329	4.4	1.0285	.....	14	..	..
13	64	276	134	0.158	0.307	4.2	1.0287	.....	16	..	..
14	64	299	134	0.169	0.352	6.1	1.0245	0.030	10	..	..
15	64	302	128	0.182	0.334	8.3	1.0223	0.028	13	..	..
16	64	306	152	0.189	0.354	10.0	1.0260	0.017	8	..	..
17	64	295	132	0.162	0.326	5.6	1.0275	0.017	16	..	..
18	70	278	144	0.198	0.404	15.6	1.0134	0.134	..	..	..
19	70	283	162	0.158	0.447	7.5	1.0207	0.058	13	..	..
20	70	284	134	0.191	0.310	16.8	1.0156	0.150	12	..	..
21	70	339	128	0.165	0.374	5.7	1.0296	0.030	19	..	..
22	87	255	174	0.197	0.315	10.0	1.0193	0.108	5	..	..
23	87	262	168	0.200	0.292	8.3	1.0195	0.092	7	..	..
24	115	278	146	0.178	0.369	4.3	1.0319	.....	19	2	I
25	115	272	148	0.173	0.467	7.2	1.0233	0.058	14	4	III
26	115	275	166	0.211	0.420	14.1	1.0160	0.152	6	4	IV
27	115	341	165	0.245	0.532	24.0	1.0160	0.322	9	4	III
28	115	272	148	0.206	0.485	13.4	1.0175	0.162	11	2	III
29	120	268	158	0.171	0.400	11.7	1.0169	0.113	5	..	..
30	121	278	158	0.161	0.484	12.1	1.0151	0.039	2	4	III
31	121	242	122	0.142	0.326	8.5	1.0189	0.030	7	..	..
32	134	282	190	0.176	0.432	9.2	1.0161	0.081	..	4	IV
33	143	383	130	0.192	0.404	10.7	1.0247	0.154	..	2	I
34	143	379	160	0.201	0.380	17.9	1.0187	0.254	..	2	I
35	143	307	140	0.188	0.365	11.5	1.0200	0.190	..	2	I
36	143	380	118	0.196	0.362	10.7	1.0280	0.114	..	2	I
37	148	275	190	0.286	0.570	9.5	1.0249	0.330	..	4	IV
38	153	312	164	0.206	0.403	10.8	1.0215	0.197	..	3	III
39	153	299	154	0.228	0.380	13.3	1.0200	0.222	..	3	II
40	153	374	142	0.212	0.580	13.2	1.0187	0.117	..	..	..
41	154	289	168	0.158	0.527	18.1	1.0139	0.159	6	4	III
42	161	268	132	0.174	0.392	5.7	1.0261	0.064	17	2	II
43	161	275	138	0.162	0.358	4.5	1.0350	0.060	18	2	II
44	161	252	118	0.159	0.362	9.4	1.0177	0.111	..	2	III
45	161	304	120	0.153	0.274	4.9	1.0271	0.013	17	1	I
46	163	286	146	0.258	0.487	27.4	1.0165	0.276	4	..	..
47	225	232	204	0.237	0.216	....	.....	.....	..	4	IV
48	225	330	174	0.228	0.543	24.3	1.0167	0.198	..	..	..
49	225	240	198	0.229	0.467	12.2	1.0156	0.134	..	..	..

graded increments of meat. A marked difference in the effect of diet is manifested in the animals which were fed the M 10 and M 20 diets, in which the urinary volumes within the normal range were 71 and 23 per cent of the total, respectively. Although the percentage distribution of urine volumes appears to be the same for the animals receiving

the M 40 and the M 80 diet, the average of the volumes for the group producing 15 cc. or more is greater in the animals receiving the M 80 diet.

Chart 4 shows the effect of diet on the specific gravity of the urine after allowance was made for the effect of proteinuria in the majority of cases. There were, however, a number of uncorrected specific gravities, and this chart represents, therefore, an approximation of the true results. It is seen that the ability to concentrate urine decreases in the animals fed the diets containing higher percentages of meat. In one case the specific gravity fell below 1.01.

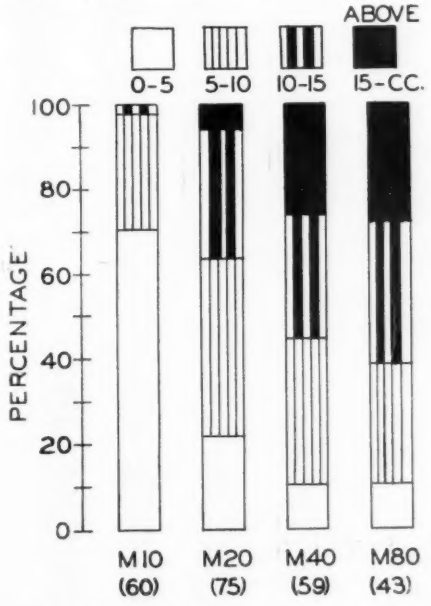

Chart 3.—The effect of diet on the urinary volume of partially nephrectomized rats.

Chart 5 summarizes the effects of diets on the excretion of protein. Of animals on the lowest meat intake, 80 per cent excreted amounts within normal limits, and the remainder did not excrete more than 0.1 Gm. The degree of proteinuria increased as the intake of meat was raised. Two animals on the M 80 diet excreted the largest amounts of protein (0.322 and 0.330 Gm.) in the entire series.

Urea Ratio: Chart 6 summarizes the urea ratio values obtained in animals shortly before they were killed (values given in tables) and values obtained at various intervals before that time. There is a decrease in the ratios, which is most marked in the animals on the M 40 and M 80 diets.

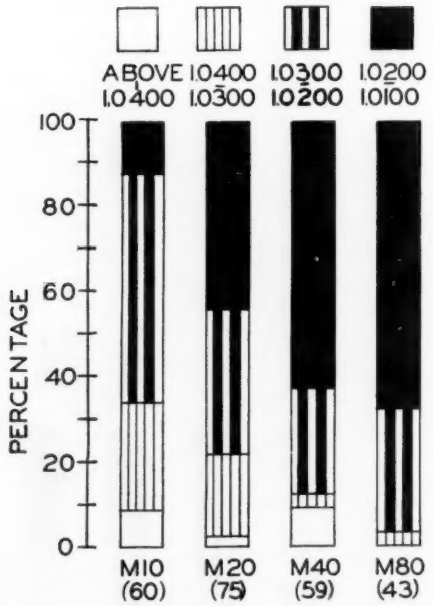

Chart 4.—The effect of diet on the specific gravity (after correction for albumin) of the urine of partially nephrectomized rats.

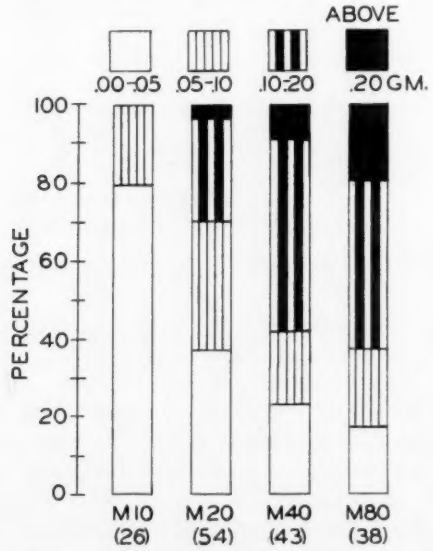

Chart 5.—The effect of diet on the excretion of protein in the partially nephrectomized rat.

The Relationship of Time After Operation to Urea Ratio: The changes in renal function were dependent on the amount of meat in the diet. Animals on the M 10 diet generally maintained a fairly uniform urea ratio over a long period of time. The group on the M 20 diet showed variations in the results, many of the ratios remaining comparatively high for a long period while others showed relatively rapid decreases in renal function. With few exceptions, the animals on both the M 40 and the M 80 diet showed rather rapid drops in the

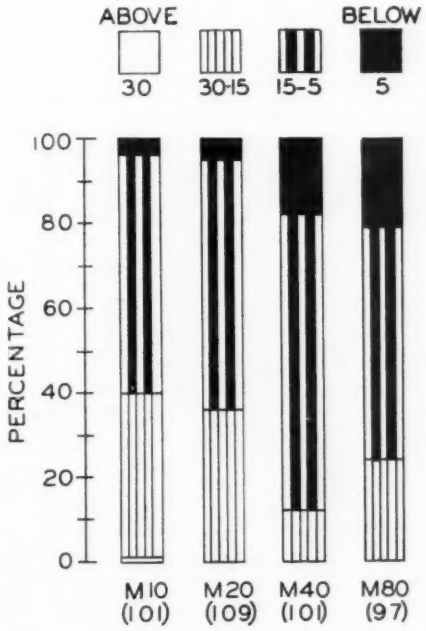

Chart 6.—The effect of diet on the Addis ratio ($\frac{\text{urea in one hour's urine}}{\text{urea in 100 cc. of blood}} \times 100$) in partially nephrectomized rats.

urea ratios. It was difficult to compare the changes in renal function at given time intervals in these animals because of the large individual variations.

When the urea ratio was determined during the first week after operation, the effect of diet was manifested during this short period. The animals on the M 40 and M 80 diets usually died shortly after the urea ratio was determined. The animals which were fed the M 20 diet were intermediate, in that some animals died and others survived, whereas none of those fed the M 10 diet died. Extremely low ratios

accompanied by high concentrations of urea were obtained in those animals which died during the "acute" period. Death was probably due to urea poisoning.

Kidneys: The variations in the $\frac{K.W.}{S.A.}$ ratios are summarized in chart 7. The averages with the standard errors were as follows: 0.179 ± 0.005, 0.245 ± 0.01, 0.289 ± 0.01 and 0.359 ± 0.014 for the groups fed the

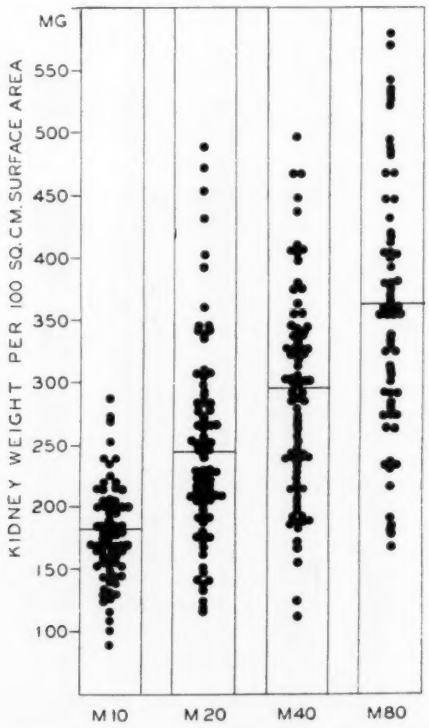

Chart 7.—The effect of diet on the $\frac{K.W.}{S.A.}$ ratio in partially nephrectomized rats.

M 10, M 20, M 40 and M 80 diets, respectively. The standard error was smallest for the group on the M 10 diet and greatest for the group on the M 80 diet, which suggests a greater reliability of the averages for the animals on the diet containing the lowest amount of meat. The greater variation in the $\frac{K.W.}{S.A.}$ ratios in the remaining groups may be due to variation in the amount of water or of renal substance or to a combination of both.

Pathologic Changes: In most of the animals with severe glomerular changes there was evidence of hypertension. The degree of proteinuria appeared to be independent of glomerular or tubular changes. There was no good correlation between the specific gravity of the urine and the degree of pathologic change. An interesting but somewhat irrelevant observation was that the adrenal glands of the animals on the M 80 diet and of the acutely ill animals on the M 40 and M 80 diets manifested marked hemorrhages in the medulla and cortex, degeneration of part of the cortex and calcareous masses in the cortex.

The Effect of Diet on Partially Nephrectomized Animals Becoming Acutely Ill.—Data for these animals are listed in table 7. The illness was either acute or chronic. Muscular tremors were usually present; occasionally convulsions were seen; the hair was ruffled, and the animal was sluggish. These animals manifested no characteristic combination of symptoms. The majority showed a marked loss of weight.

The blood pressure varied from 50 to 232 mm. of mercury. In all animals with low blood pressure there was evidence of previous hypertension as manifested by dilated arteries and hypertrophied hearts. In calculating the $\frac{\text{H. W.}}{\text{S. A.}}$ ratios of these animals, no correction was made for the loss of weight. It should be noted that many of the $\frac{\text{K. W.}}{\text{S. A.}}$ ratios were particularly low, especially in the M 80 group. In practically every instance in which the concentration test was made, there was a consistently low value for renal function. Only two urea ratios were available, but other data suggest that low ratios are typical of the last stages of this syndrome. The pathologic findings indicated severe renal damage in all the dietary groups. In practically all rats fed the M 80 diet there were gross manifestations of hemorrhage in the adrenal glands, varying from a multiple punctate appearance to an almost solid red appearance.

COMMENT

When the relative effects of various percentages of liver [1b] and of meat in the diets of partially nephrectomized animals are compared, the experimental procedure and the nitrogen content of the respective diets being essentially the same, it will be seen that: The variations in the urinary volume and specific gravity are not different; the excretion of protein was slightly greater for rats on several of the meat diets, and hypertension was more pronounced and frequent only in the rats fed the diets containing the highest percentage of meat. Since these differences observed in animals on the meat and liver diets were not uniform or striking, it was concluded that these diets have essentially the same effect on the renal function of partially nephrectomized rats.

TABLE 7.—*Partially Nephrectomized Animals Killed While Acutely Ill*

Rat	Duration of Experiment, Days	Surface Area, Sq. Cm.	Blood Pressure, Mm.	Heart Weight / Surface Area × 100	Kidney Weight / Surface Area × 100	Twenty-Four Hour Urine Concentration Test: Volume, Cc.	Specific Gravity	Albumin, Gm.	Urea Ratio	Pathologic Change: Tubule	Glomerulus
					M 10						
1	115	220	98	0.202	0.136	....	.....	.....	..	..	..
2	134	223	180	0.270	0.240	....	.....	.....	..	..	..
3	140	281	170	0.229	0.185	....	.....	.....	..	..	..
4	143	244	120	0.210	0.205	....	.....	.....	..	..	..
5	192	246	114	0.275	0.194	....	.....	.....	..	4	IV
6	219	270	148	0.272	0.168	....	.....	.....	..	..	..
					M 20						
1	34	242	202	0.246	0.142	....	.....	.....	..	..	..
2	71	255	66	0.282	0.247	5.0	1.0267	0.003	9	..	..
3	87	257	98	0.230	0.253	....	.....	.....	..	2	III
4	101	254	66	0.214	0.278	....	.....	.....	..	3	II
5	101	291	196	0.279	0.402	....	.....	.....	..	3	III
6	106	358	174	0.254	0.177	....	.....	.....	..	..	..
7	107	345	228	0.258	0.267	....	.....	.....	..	..	..
8	109	363	138	0.253	0.311	....	.....	.....	..	3	III
9	123	339	206	0.256	0.453	....	.....	.....	..	3	III
10	124	292	110	0.289	0.472	....	.....	.....	..	3	..
11	126	355	124	0.254	0.346	....	.....	.....	..	..	..
12	129	242	106	0.247	0.264	....	.....	.....	..	..	..
13	157	354	232	.....	.....	....	.....	.....	..	4	IV
14	167	373	216	0.246	0.340	....	.....	.....	..	3	IV
15	168	334	222	0.247	0.266	....	.....	.....	..	4	III
16	202	390	164	0.249	0.229	13.9	1.0162	0.106	5	..	..
17	238	332	76	0.238	0.256	....	.....	.....	..	..	..
18	239	335	176	0.294	0.284	....	.....	.....	..	..	..
19	291	392	156	0.321	0.338	....	.....	.....	..	..	..
					M 40						
1	13	212	106	0.134	0.112	....	.....	.....	..	..	..
2	32	171	96	0.181	0.214	....	.....	.....	..	..	..
3	57	244	118	0.227	0.410	....	.....	.....	..	..	..
4	79	346	206	0.230	0.244	....	.....	.....	..	..	..
5	79	250	174	0.256	0.125	....	.....	.....	..	..	..
6	79	349	196	0.247	0.328	....	.....	.....	..	..	..
7	81	355	194	0.146	0.448	....	.....	.....	..	..	..
8	87	243	164	0.216	0.189	....	.....	.....	..	..	..
9	92	306	194	0.257	0.374	....	.....	.....	..	..	..
10	94	298	150	0.258	0.240	....	.....	.....	..	..	..
11	118	324	120	0.246	0.191	....	.....	.....	..	..	..
12	125	334	180	0.254	0.320	....	.....	.....	..	..	..
13	128	363	166	0.231	0.380	....	.....	.....	..	..	..
14	136	314	64	0.278	0.228	....	.....	.....	..	..	..
15	139	349	160	0.266	0.307	....	.....	.....	..	..	..
16	150	339	80	0.264	0.329	....	.....	.....	..	..	..
17	179	289	66	0.224	0.467	19.0	1.0195	0.260	..	..	..
					M 80						
1	37	238	104	0.163	0.283	....	.....	.....	..	1	I
2	52	272	...	0.218	0.274	....	.....	.....	..	..	..
3	53	282	44	0.239	0.378	....	.....	.....	..	4	IV
4	56	217	50	0.219	0.191	....	.....	.....	..	4	IV
5	56	289	166	0.258	0.232	17.0	1.0173	0.172	..	3	II
6	57	282	48	0.206	0.185	18.0	1.0173	0.266	..	4	III
7	57	246	196	0.219	0.178	12.3	1.0180	.....	..	4	IV
8	57	270	186	0.254	0.181	14.7	1.0149	0.082	..	4	II
9	58	216	150	.....	.....	....	.....	.....	..	..	..
10	63	281	152	0.213	0.360	....	.....	.....	..	..	..
11	77	245	118	0.248	0.361	....	.....	.....	..	3	II
12	77	291	216	0.215	0.535	....	.....	.....	..	..	..
13	81	257	178	0.218	0.273	....	.....	.....	..	..	..
14	85	296	76	0.261	0.413	....	.....	.....	..	..	..
15	93	314	136	0.236	0.526	....	.....	.....	..	4	III
16	94	227	170	0.165	0.167	....	.....	.....	..	..	..
17	112	270	194	0.242	0.418	....	.....	.....	..	4	IV
18	119	214	34	0.268	0.234	....	.....	.....	..	..	..
19	126	267	98	0.262	0.301	....	.....	.....	..	3	III
20	135	274	80	0.223	0.360	....	.....	.....	..	4	IV
21	135	218	94	0.210	0.494	....	.....	.....	..	..	..
22	143	299	184	0.307	0.447	18.0	1.0151	0.196	..	4	IV

It has been demonstrated [8] that hypertrophy was proportional to protein (casein) consumption, and a formula expressing the relationship of protein consumption to kidney weight per unit of surface area was presented. MacKay and MacKay [9] and Wilson [10] recently observed that the degree of renal hypertrophy was influenced by the type of protein fed. In the present study the consumption of food was not measured, and the quantitative relationship between the intake of food and the size of the kidneys could not be made. Since the nitrogen content of the various meat and liver diets [1b] was not exactly the same, a comparison of the $\frac{K.W.}{S.A.}$ ratios can best be made at the same nitrogen concentration of the two diets. The influence of liver and meat diets on the hypertrophy of the kidneys of the partially nephrectomized, unilaterally nephrectomized and intact control animals has been com-

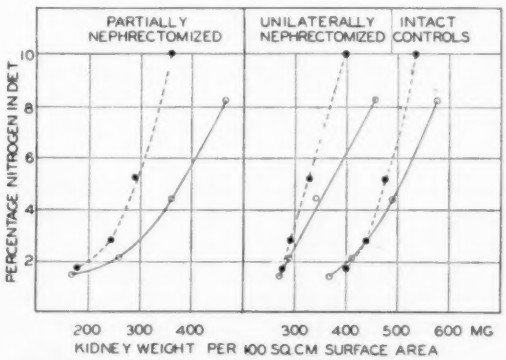

Chart 8.—The influence of diets containing meat and liver on the $\frac{K.W.}{S.A.}$ ratios of partially nephrectomized, unilaterally nephrectomized and intact rats. The broken line indicates the animals on diets containing meat. The solid line indicates those on diets containing liver.

pared in chart 8. With increasing amounts of protein, liver diets cause a progressively more marked hypertrophy, especially in the partially nephrectomized animals.

It has been shown by a number of workers that the urea ratio in normal human beings and animals is elevated immediately after the

8. MacKay, E. M.; MacKay, L. L., and Addis, T.: Am. J. Physiol. **86**:459, 1928.

9. MacKay, E. M., and MacKay, L. L.: J. Nutrition **8**:187, 1934.

10. Wilson, H. E. C.: Biochem. J. **27**:1348, 1933.

ingestion of a meal containing protein.[11] The maximal postprandial ratios were obtained in animals maintained on a meat diet.[12] The lowest ratios were noted in human beings and animals on a low protein diet.[13] In four cases of hemorrhagic Bright's disease, Keutmann and McCann [14] noted slight increases in the functional capacity of the kidney, as measured by urea clearance after a liberal protein intake. Cope [15] found a depression of the clearance in persons with nephritis with normal or nearly normal function after lowering the basal protein intake. Raising the protein intake of these patients had no consistent effect on the urea clearance. In patients with depressed renal function, the clearance appeared to be fixed and was not appreciably influenced by the amount of protein fed. Pitts [12] expressed the belief that the primary effect of protein on normal renal function is due to the action of amino-acids on glomerular activity. Van Slyke and his co-workers [16] demonstrated that the urea clearance varied in direct proportion to renal blood flow. In the present study, a quantitative relationship between the urea ratio and the amount of dietary protein has been shown for unilaterally nephrectomized and intact rats. Continued ingestion of diets high in protein tends to decrease the ratio in partially nephrectomized animals. No evidence is available to explain the changes in renal function due to the effect of diet.

When an animal with a small remnant of kidney is given a diet containing a comparatively low percentage of protein (M 10 or L 10), the renal function is maintained at a fairly good level for a long time without the development of azotemia or of any marked degree of hypertension. A small increase in the amount of nitrogen of the diet (M 20 or L 20) causes marked pathologic changes and loss of renal function. Although the latter diets are considered to have protein concentrations which are minimal for the maintenance of intact rats, the reduced renal tissue of the partially nephrectomized rats seems to have reacted as to a definitely increased metabolic load. The cause of this difference in animals ingesting additional small amounts of meat or liver is not

11. (*a*) Addis, T., and Drury, D. R.: J. Biol. Chem. **55**:629, 1923. (*b*) Jolliffe, N., and Smith, H. W.: Am. J. Physiol. **99**:101, 1931. (*c*) Shannon, J. A.; Jolliffe, N., and Smith, H. W.: ibid. **101**:625, 1932. (*d*) Van Slyke, D. D.; Rhoads, C. P.; Hiller, A., and Alving, A.: Relationship of Urea Clearance to Renal Blood Flow, ibid. **110**:387 (Dec.) 1934.

12. Pitts, R. F.: J. Nutrition **9**:657, 1935. Shannon and others.[11c]

13. Goldring, W.; Razinsky, L.; Greenblatt, M., and Cohen, S.: J. Clin. Investigation **13**:743, 1934. Shannon and others.[11c]

14. Keutmann, E. H., and McCann, W. S.: J. Clin. Investigation **11**:973, 1932.

15. Cope, C. L.: J. Clin. Investigation **12**:567, 1933.

16. Van Slyke, D. D.; Rhoads, C. P.; Hiller, A., and Alving, A.: Relationships Between Urea Excretion, Renal Blood Flow, Renal Oxygen Consumption and Diuresis: Mechanism of Urea Excretion, Am. J. Physiol. **109**:336 (Aug.) 1934.

clear. Apparently the changes must be due either to the excretion of injurious products of protein breakdown, such as amino-acids,[17] to the effect of water-soluble nitrogenous extractives [18] or to the extra burden involved in the excretion of nitrogen metabolites per se.

The effects of diets high in protein on the kidneys of experimental animals has recently been reviewed.[19] The work of Newburgh and Curtis [20] is striking, since they reported renal damage when diets rich in liver, other meat and casein were fed to white rats with intact kidneys for a prolonged period. Liver produced the greatest damage in the shortest time; renal injury caused by other meat was not as marked and required a longer time for its production. It was believed these renal changes could be best explained by the differences in the amino-acid composition of the proteins fed. In a later report Newburgh and Johnston [18] postulated that the water-soluble extractives of liver and meat were responsible for the marked renal changes because when they fed sodium nucleate, pronounced renal damage was produced by comparatively small amounts of the material. After reduction of the renal tissue by unilateral nephrectomy, casein fed in high concentrations caused glomerular and tubular changes in a relatively short time.[21] Further reduction of renal tissue by partial nephrectomy caused pathologic changes very soon after operation in animals fed a standard diet containing 20 per cent of extracted meat.[1a] The effect of dietary protein on the kidney varies, therefore, with the type of protein fed and with the relative renal reserve.

In recent years attention has been called to the importance of feeding adequate amounts of protein to patients with certain types of renal disease.[22] It has been recognized that patients losing large amounts of protein in the urine must be fed relatively large amounts in an effort to maintain nitrogen equilibrium. Experimentation with animals has demonstrated that not only the quantity but the quality of protein foods is of importance in the production of renal injury. It has been shown, for example, that there is a great difference between the renal damage produced by diets rich in whole liver and that produced by liver washed free of water-soluble constituents.[1b] The qualitative aspects of protein

17. Newburgh, L. H., and Marsh, P. L.: Renal Injuries by Amino Acids, Arch. Int. Med. **36**:682 (Nov.) 1925.

18. Newburgh, L. H., and Johnston, M. W.: J. Clin. Investigation **10**:153, 1931.

19. Mitchell, H. H.: J. Nutrition **1**:271, 1929. Bischoff, Fritz: ibid. **5**:431, 1932.

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feeding must be stressed. Although protein per se may be a factor in producing renal lesions under strain, the nephrotoxic substances associated with protein foods must be seriously considered if there is any analogy between experimental animals and patients with renal lesions. Such factors as the amino-acid composition of the protein,[15] the non-protein constituents,[19] the products of purine metabolism [18] and the presence of excess phosphate precursors [23] and possibly of other substances may play an important rôle in the dietary regimen of the patient with disturbed renal function. Work in this laboratory is being continued with partially nephrectomized animals to determine the relationship between renal damage and the type of protein ingested.

SUMMARY

The effect of feeding diets containing various percentages (10, 20, 40 and 80) of whole dried meat to rats with intact kidneys and to unilaterally nephrectomized and partially nephrectomized rats has been studied.

The ingestion of these diets by intact and by unilaterally nephrectomized animals caused a progressive enlargement of the kidneys. When the kidneys of the rats on the M 10 diet were used as a standard, the degree of hypertrophy was the same for the control groups on both the M 20 and the M 40 diet. The kidneys of the animals on the M 80 diet showed a marked degree of hypertrophy, particularly in the unilaterally nephrectomized animals.

The syndrome in the partially nephrectomized rats was affected by the percentage of the whole meat in the diet in the following manner:

1. The frequency and the degree of hypertension became more pronounced as the content of whole meat in the diet was increased. A substantial relationship was demonstrated for the majority of the dietary groups between the blood pressure and the $\frac{\text{H. W.}}{\text{S. A.}}$ ratio.

2. A progressively increased volume of dilute urine was excreted during a concentration test as the percentage of meat in the diet was raised. This increased renal insufficiency was confirmed by a lowering of the urea ratio: $\frac{\text{urea excreted per hour}}{\text{urea in 100 cc. of blood}}$

The pathologic changes were progressively exaggerated in the kidney remnant with the increase in the concentration of meat in the diet.

The average weight of the remnant of kidney increased with the increased concentration of meat and was accompanied by greater individual variations.

No immediate clinical application of these results can be made. The possible importance of the type of protein ingested by man and by animals with renal insufficiency has been considered.

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EXPERIMENTAL RENAL INSUFFICIENCY PRODUCED BY PARTIAL NEPHRECTOMY

VI. THE RELATION BETWEEN KIDNEY FUNCTION, KIDNEY WEIGHT AND SURFACE AREA IN INTACT AND UNILATERALLY NEPHRECTOMIZED RATS FED WHOLE DRIED MEAT DIETS

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The determination of the urea ratio, $\frac{\text{urea in 1 hour's urine}}{\text{urea in 100 cc. of blood}}$, of Addis and his collaborators [1] has proved to be a satisfactory method for the estimation of the percentage of functioning renal tissue. It was found to be the best functional test to give an approximation of the quantitative and structural changes caused by unilateral nephrectomy [2] and by uranium "nephritis." [3] The magnitude of the Addis ratio was found to be directly related to the size of the kidneys in intact rats,[4] in rabbits [5] and in human beings.[6] A relationship between the urea ratio and the surface area in the dog [7] and in man [6] has been demonstrated. It has also been shown that a relationship exists between the area of the body surface and kidney weight in the rat,[8] the rabbit,[5] the dog [9] and man.[6] It would appear that renal function, kidney weight

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and body surface are all directly related to one another in man and in experimental animals. The aforementioned experiments have been performed on both intact and unilaterally nephrectomized animals maintained on standard diets. It is our purpose in this paper to consider the effect of dietary changes on the $\frac{\text{urea ratio}}{\text{kidney weight}}$, $\frac{\text{kidney weight}}{\text{surface area}}$ and $\frac{\text{urea ratio}}{\text{surface area}}$ ratios in intact and in unilaterally nephrectomized rats.

This study was based on an analysis of part of the data already presented.[10] Only animals on which complete data were available were included in the present analysis, and hence the average figures are not identical with the figures previously reported.[10] The experimental procedures, experimental diets and abbreviations were outlined.[10]

RESULTS

Intact Animals.—The $\frac{\text{K.W.}}{\text{S.A.}}$ ratio, kidney weight, surface area, Addis ratio, $\frac{\text{urea ratio}}{\text{kidney weight}}$ ratio and $\frac{\text{urea ratio}}{\text{surface area}}$ ratios obtained in the intact rats on diets containing percentages of various whole meat are presented in table 1. It will be seen that the average urea ratio and the average kidney weight per hundred square centimeters of body surface increased with the greater percentage of whole meat in the diet. It is significant that almost identical average values for the urea ratio per gram of kidney tissue (36.3, 36.9, 35.6 and 37.6) were obtained in these animals on diets containing, respectively, 10, 20, 40 and 80 per cent of whole dried meat. The respective average urea ratios per hundred square centimeters of body surface for the dietary groups were 0.144, 0.158, 0.184 and 0.206, which with the ratio for the group receiving the M10 diet as unity represents a proportion of 1, 1.08, 1.20 and 1.32, respectively. In a similar manner the proportionate increase in the $\frac{\text{K.W.}}{\text{S.A.}}$ ratios was 1, 1.10, 1.28 and 1.43 for the respective diets.

Unilaterally Nephrectomized Animals.—The data for the individual unilaterally nephrectomized rats are presented in table 2. The average values for the urea ratio per gram of kidney tissue were 38.3, 40.7, 36.6 and 36 for the respective dietary groups. The respective average urea ratios per hundred square centimeters of body surface for these groups were 0.111, 0.119, 0.126 and 0.145, which represent a proportion of 1, 1.07, 1.13 and 1.31. In a similar manner the proportionate increase in the $\frac{\text{K. W.}}{\text{S. A.}}$ ratios was 1, 1, 1.17 and 1.37, respectively.

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TABLE 1.—*Observations on Intact Rats*

Rat	Duration of Experiment, Days	Kidney Weight / Surface Area × 100	Kidney Weight, Gm.	Urea Ratio: Urine Rate / Blood Concentration × 100	Surface Area, Sq. Cm.	Urea Ratio / Kidney Weight	Urea Ratio / Surface Area
			M 10				
1	44	0.425	1.514	50	356	33.0	0.141
2	44	0.430	1.697	61	386	36.0	0.158
3	44	0.419	1.456	60	348	41.2	0.172
4	44	0.360	1.083	62	302	57.1	0.205
5	44	0.374	1.056	55	283	52.0	0.195
6	44	0.382	1.126	50	295	44.5	0.170
7	44	0.383	1.237	43	323	34.8	0.133
8	44	0.408	1.401	70	343	50.0	0.204
9	59	0.424	1.602	65	379	40.5	0.172
10	59	0.380	1.275	48	336	37.6	0.143
11	59	0.444	1.571	36	354	22.9	0.102
12	61	0.482	1.749	28	362	16.0	0.077
13	61	0.495	1.753	34	354	19.3	0.096
14	61	0.433	1.369	47	316	34.4	0.149
15	61	0.425	1.637	58	386	35.4	0.150
16	142	0.344	1.016	44	295	43.3	0.149
17	146	0.342	1.350	34	396	25.2	0.086
18	147	0.377	1.405	38	373	26.2	0.102
19	155	0.368	1.509	38	412	27.0	0.092
20	203	0.453	1.886	69	415	36.6	0.166
21	203	0.328	1.138	48	345	42.2	0.139
22	226	0.394	1.340	59	340	44.0	0.173
Average.....		0.403		50		36.3	0.144
			M 20				
23	37	0.392	1.121	54	286	48.0	0.188
24	37	0.388	1.191	52	307	43.6	0.169
25	37	0.468	1.702	60	364	35.2	0.165
26	37	0.435	1.613	60	370	37.2	0.162
27	37	0.393	1.179	59	300	50.0	0.197
28	37	0.483	1.810	67	375	37.0	0.179
29	37	0.492	1.850	48	376	25.9	0.128
30	52	0.483	1.803	55	374	30.4	0.147
31	52	0.550	2.018	63	366	31.2	0.173
32	52	0.499	1.995	80	400	40.0	0.200
33	52	0.469	1.689	53	300	31.4	0.177
34	52	0.426	1.839	53	386	28.8	0.137
35	105	0.485	2.017	62	415	30.8	0.150
36	118	0.412	1.494	35	364	23.4	0.096
37	122	0.252	1.117	74	442	66.3	0.168
38	146	0.350	1.080	51	308	47.2	0.165
39	153	0.418	1.439	43	344	29 9	0.125
40	178	0.368	1.252	51	340	40.7	0.150
41	183	0.472	1.934	75	410	38.8	0.183
42	207	0.472	2.265	79	478	34.8	0.165
43	207	0.434	1.620	42	373	25.9	0.113
44	217	0.422	1.735	60	412	34.6	0.146
Average.....		0.435		58		36.9	0.158
			M 40				
45	38	0.478	1.786	67	374	37.5	0.179
46	38	0.470	1.680	61	358	36.3	0.171
47	38	0.439	1.240	42	283	33.8	0.148
48	38	0.515	2.013	64	391	31.8	0.164
49	38	0.535	2.096	74	392	35.3	0.188
50	38	0.506	1.921	76	380	39.5	0.200
51	38	0.502	1.778	57	354	32.1	0.161
52	53	0.623	2.334	67	286	28.7	0.178
53	53	0.541	2.089	74	300	35.4	0.246
54	53	0.573	2.173	82	294	37.7	0.278
55	53	0.469	1.392	62	194	44.6	0.320
56	66	0.390	1.135	30	291	26.4	0.103
57	84	0.430	1.588	54	369	34.1	0.147
58	134	0.350	1.167	48	333	41.2	0.144
59	141	0.470	1.870	67	398	35.8	0.168
60	149	0.435	1.785	60	410	33.6	0.146
Average.....		0.483		62		35.2	0.184

TABLE 1.—*Observations on Intact Rats—Continued*

Rat	Duration of Experiment, Days	Kidney Weight / Surface Area × 100	Kidney Weight, Gm.	Urea Ratio: Urine Rate / Blood Concentration × 100	Surface Area, Sq. Cm.	Urea Ratio / Kidney Weight	Urea Ratio / Surface Area
			M 80				
61	38	0.545	1.630	59	297	36.2	0.198
62	38	0.570	2.072	70	362	33.8	0.193
63	38	0.544	1.587	56	292	35.3	0.143
64	38	0.495	1.492	82	302	54.9	0.271
65	38	0.615	2.261	61	368	27.0	0.166
66	38	0.648	1.886	103	291	54.7	0.354
67	53	0.550	1.997	69	364	34.6	0.189
68	53	0.535	1.590	67	297	42.2	0.226
69	53	0.630	2.520	64	402	25.4	0.159
70	53	0.602	2.255	96	374	42.5	0.256
71	53	0.600	2.067	87	345	42.0	0.252
72	53	0.530	1.595	63	302	39.5	0.208
73	53	0.610	2.105	81	346	40.3	0.234
74	64	0.532	1.810	47	341	25.9	0.138
75	115	0.556	1.702	60	307	35.2	0.196
76	120	0.532	2.135	84	402	39.4	0.209
77	161	0.510	1.555	75	304	48.2	0.247
78	191	0.537	1.716	51	320	29.7	0.159
79	203	0.547	2.170	83	397	38.2	0.209
80	203	0.485	1.620	61	334	37.6	0.183
81	377	0.530	1.712	47	323	27.4	0.145
Average.....		0.533		69		37.6	0.206

TABLE 2.—*Observations on Unilaterally Nephrectomized Rats*

Rat	Duration of Experiment, Days	Kidney Weight / Surface Area × 100	Kidney Weight, Gm.	Urea Ratio: Urine Rate / Blood Concentration × 100	Surface Area, Sq. Cm.	Urea Ratio / Kidney Weight	Urea Ratio / Surface Area
			M 10				
1	35	0.278	0.934	38	336	40.7	0.113
2	35	0.270	0.901	36	334	39.9	0.108
3	35	0.240	0.680	27	283	39.7	0.095
4	35	0.277	0.868	35	313	40.3	0.112
5	35	0.300	1.084	35	362	32.2	0.097
6	50	0.295	1.093	33	370	30.2	0.089
7	50	0.378	1.116	47	376	42.2	0.125
8	50	0.316	1.196	43	379	36.0	0.113
9	50	0.354	1.074	46	304	42.8	0.151
10	50	0.300	1.115	52	372	46.7	0.140
11	50	0.276	0.756	32	274	42.3	0.117
12	101	0.327	1.125	41	345	36.4	0.119
13	142	0.264	0.724	31	274	42.8	0.113
14	142	0.300	0.870	42	289	48.3	0.145
15	146	0.238	1.020	33	428	32.4	0.077
16	147	0.264	0.830	23	314	27.7	0.073
17	152	0.322	1.254	38	389	30.1	0.098
Average.....		0.294		37		38.3	0.111
			M 20				
18	35	0.274	0.838	51	306	61.0	0.167
19	35	0.289	0.865	34	299	39.3	0.114
20	35	0.332	1.381	43	417	31.1	0.103
21	35	0.332	1.244	43	375	34.6	0.115
22	35	0.314	1.250	54	398	43.3	0.136
23	35	0.308	1.095	40	356	36.5	0.112
24	35	0.288	0.991	35	345	35.3	0.102
25	50	0.306	1.149	38	376	33.0	0.101
26	50	0.328	1.200	45	366	37.5	0.123
27	50	0.264	0.797	42	302	52.7	0.139
28	50	0.263	0.794	37	302	46.6	0.123
29	50	0.277	0.842	38	304	45.1	0.125
30	90	0.320	1.252	50	392	39.9	0.128
31	106	0.332	1.245	35	376	27.1	0.093
32	113	0.252	0.734	29	291	39.6	0.099
33	120	0.254	0.803	40	305	50.0	0.131
34	154	0.324	1.468	59	453	40.3	0.130
35	166	0.304	1.300	65	428	50.0	0.152
36	166	0.291	1.200	50	413	41.7	0.121
37	202	0.270	0.941	35	348	37.0	0.101
38	207	0.288	0.985	32	341	32.5	0.094
Average.....		0.295		42		40.7	0.119

TABLE 2.—*Observations on Unilaterally Nephrectomized Rats—Continued*

Rat	Duration of Experiment, Days	Kidney Weight / Surface Area × 100	Kidney Weight, Gm.	Urea Ratio: Urine Rate / Blood Concentration × 100	Surface Area, Sq. Cm.	Urea Ratio / Kidney Weight	Urea Ratio / Surface Area
			M 40				
39	41	0.378	1.484	45	392	30.3	0.115
40	41	0.370	1.310	46	354	35.0	0.130
41	41	0.316	0.906	38	286	42.0	0.138
42	41	0.372	1.327	55	356	41.5	0.154
43	41	0.368	1.229	50	334	40.7	0.150
44	41	0.314	0.805	28	256	34.8	0.110
45	41	0.374	1.303	46	348	35.2	0.132
46	43	0.346	0.950	38	274	40.0	0.139
47	43	0.352	0.976	33	277	33.8	0.119
48	43	0.370	1.310	55	354	42.0	0.155
49	66	0.327	1.200	43	366	35.8	0.118
50	84	0.338	1.392	45	412	32.3	0.109
51	84	0.362	1.333	51	370	38.2	0.138
52	129	0.308	1.180	36	390	30.5	0.092
53	134	0.340	1.405	50	413	35.6	0.121
54	176	0.264	0.770	30	292	39.0	0.103
Average.....		0.343		43		36.6	0.126
			M 80				
55	41	0.334	0.863	33	258	38.2	0.128
56	41	0.418	1.425	59	341	41.3	0.173
57	41	0.347	0.923	40	266	43.3	0.150
58	41	0.385	1.032	36	268	34.8	0.134
59	43	0.435	1.513	48	348	31.7	0.138
60	43	0.435	1.633	51	376	31.2	0.135
61	43	0.418	1.376	66	318	48.0	0.208
62	43	0.405	1.363	71	334	52.0	0.212
63	43	0.432	1.160	47	268	40.5	0.175
64	43	0.430	1.410	54	328	38.3	0.164
65	43	0.465	1.580	70	340	44.2	0.206
66	43	0.474	1.615	55	341	34.1	0.162
67	70	0.428	1.622	61	379	37.6	0.161
68	87	0.447	1.733	46	389	26.6	0.118
69	87	0.361	1.184	23	328	19.4	0.070
70	121	0.427	1.685	46	397	27.3	0.116
71	143	0.396	1.462	42	379	28.7	0.111
72	161	0.328	1.029	39	313	38.0	0.125
73	162	0.387	1.074	31	278	28.8	0.111
74	206	0.358	1.219	50	339	41.0	0.147
75	206	0.364	1.219	54	333	44.3	0.162
76	225	0.382	1.170	27	306	23.1	0.088
Average.....		0.402		48		36.0	0.145

COMMENT

It is striking that almost identical average values for the urea ratio per gram of kidney tissue were obtained for all eight groups of rats studied. The average values for the $\frac{\text{urea ratio}}{\text{kidney weight}}$ ratio were 36.5 and 37.9 for all the intact and all the unilaterally nephrectomized rats, respectively. Because of the close relationship between the kidney weight and the urea ratio in the animals with one and two kidneys, the data for both groups were combined and presented diagrammatically in chart 1. The percentage of the mean normal value for the urea ratio was calculated for the dietary groups from the average ratio obtained in the intact animals of the respective group. The statistical reliability of these $\frac{\text{urea ratio}}{\text{kidney weight}}$ ratios for the various dietary groups was obtained by determining the correlation coefficients and the probable errors as follows: M10, 0.41 ± 0.089; M20, 0.69 ± 0.053; M40, 0.86 ± 0.030; and M80, 0.65 ± 0.059. There is a high relationship for

the group receiving the M40 diet, a marked relationship for the groups receiving the M20 and M80 diets and a low correlation for the group on the M10 diet. These findings indicate that the variation or constancy of the urea ratio per unit of kidney weight is dependent on the protein intake.

MacKay and Raulston [4] demonstrated a constant urea ratio per gram of kidney tissue in intact normal rats of different ages and sizes fed a

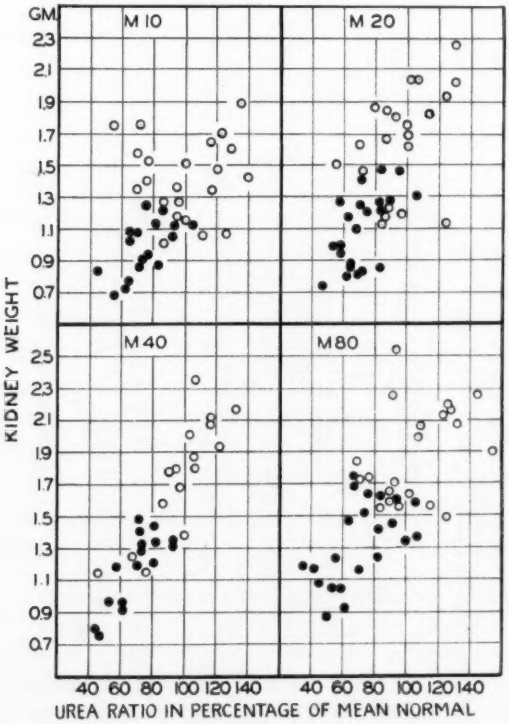

Chart 1.—Relation between kidney weight and urea (Addis) ratio. In charts 1 and 2 the unshaded circles indicate rats with both kidneys intact, and the shaded circles indicate those with only one kidney.

standard diet. This finding has been confirmed and extended to show that this relationship is constant despite the effect of diet on renal hypertrophy on the animals with one and two kidneys. From the data given in the previous paper,[10] it can be seen that the partially nephrectomized rats in which renal damage developed show absolutely no constancy in this relationship.

It has been demonstrated that there is a direct relationship between the kidney weight and the surface area in intact rats on a standard diet.[8] It is obvious from chart 2 that this has been confirmed for rats with two kidneys on a nitrogen intake similar to that obtained from the standard diet. In addition it can be seen that there is a direct rela-

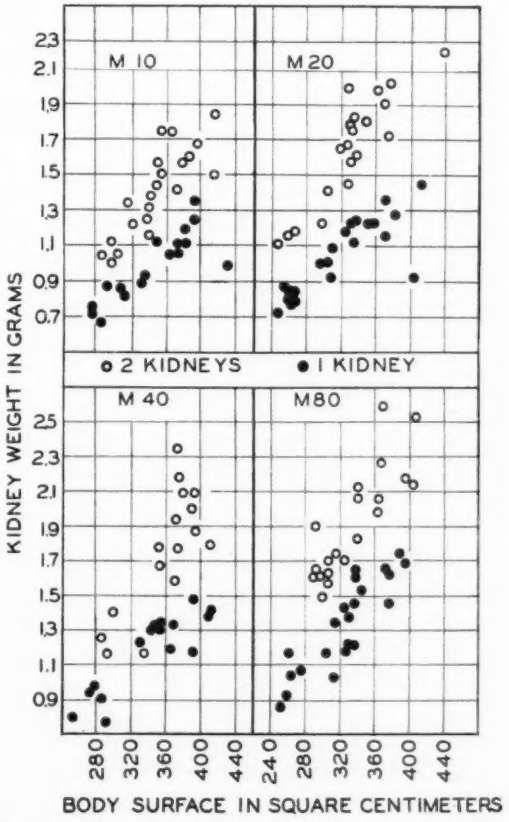

Chart 2.—The relation of kidney weight to surface area.

tionship for all diets but the ratios are not the same. Furthermore, there is the same kind of direct relationship for the unilaterally nephrectomized animals, but in these rats a unit of kidney weight corresponds to a greater surface area.

The direct relation of renal function to body surface and kidney weight in man and in animals has been reviewed by MacKay.[6] In

the present paper, it is shown that the urea ratio is proportional to the surface area if the degree of renal hypertrophy is considered. In the rat, therefore, one cannot use body surface as an index of renal function unless a factor is used which makes allowance for the dietary regimen. It is reasonable to assume that this holds true for other experimental animals and for man.

SUMMARY

The relation between kidney weight, surface area and the urea (Addis) ratio, $\frac{\text{urea excreted per hour}}{\text{urea in 100 cc. of blood}}$, was compared in intact and unilaterally nephrectomized rats fed diets containing 10, 20, 40 and 80 per cent of whole dried meat.

It was shown that the weight of the kidneys is directly related to the surface area in the animals ingesting diets containing different concentrations of protein.

The ratio $\frac{\text{urea ratio}}{\text{kidney weight}}$ is constant for these animals on all dietary groups. The highest degree of correlation for this ratio was found in the group ingesting 40 per cent of whole meat.

The values for the $\frac{\text{urea ratio}}{\text{surface area}}$ ratio increased in both the intact and the unilaterally nephrectomized animals with the added increments of whole meat in the diet. These values were proportional to the degree of renal hypertrophy. Renal function can be estimated in these animals provided the urea ratio for a given diet is known.

EXPERIMENTAL RENAL INSUFFICIENCY PRODUCED BY PARTIAL NEPHRECTOMY

VII. THE RELATIONSHIP OF URINE UREA, BLOOD UREA AND UREA (ADDIS) RATIO IN RATS ON WHOLE DRIED MEAT DIETS

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The present study deals with the effect of feeding diets containing various concentrations of whole meat on the amount of urea in the urine and blood and the urea (Addis) ratio, $\frac{\text{urea excreted}}{\text{blood urea}}$ in partially nephrectomized, unilaterally nephrectomized and intact rats.

The experimental procedure, the experimental diets and abbreviations were outlined in a previous paper.[1] The data for all animals excreting less than 50 per cent of the urea solution administered were excluded. The previous data have been supplemented by values obtained at frequent intervals in individual animals.

RESULTS

The effect of various concentrations of whole dried meat on the amount of urea in the blood and urine and on the urea ratio, $\frac{\text{urea excreted per hour}}{\text{urea in 100 cc. blood}} \times 100$, of partially nephrectomized and control animals (unilaterally nephrectomized and intact) is shown in chart 1. Five phases of renal function are indicated by the oblique lines, representing calculated urea ratios of 5, 10, 15, 20 and 60, which are indicative of stages from severe renal insufficiency to normal function. It can be seen that among the partially nephrectomized rats the percentage incidence of marked renal insufficiency in the group receiving the M 80 diet

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From the Laboratory of Physiological Chemistry, the University of Virginia.

This investigation was made possible by a grant from the National Live Stock and Meat Board and by the Edward N. Gibbs Prize Fund of the New York Academy of Medicine.

The statistical analyses were performed by Dr. Williams, who is on the staff of the Leander McCormick Observatory.

1. Chanutin, A., and Ludewig, S.: Experimental Renal Insufficiency Produced by Partial Nephrectomy: V. Diets Containing Whole Dried Meat, Arch. Int. Med., this issue, p. 60.

is four times as great as that in the group on the M 10 diet and, conversely, the percentage of cases in which the ratio was above 20 is greater for the animals receiving lower protein diets.

An unadjusted and an adjusted curve are shown on the diagrams of the groups on the M 20, M 40 and M 80 diets; these two curves are identical for the group on the M 10 diet. Each unadjusted curve has been drawn midway between the two regression curves obtained in the standard statistical manner for the particular group.

From the dispersion of the individual points around the curve, it was found that in the case of the animals on the M 10 diet the probable

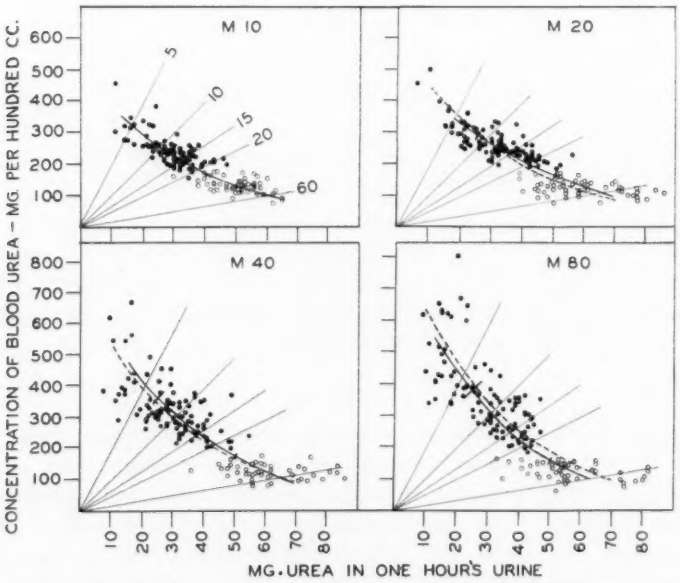

Chart 1.—The relation of blood urea and urine urea in partially nephrectomized, intact and unilaterally nephrectomized rats. The oblique lines represent the urea ratio, $\frac{\text{urea excreted}}{\text{blood urea}} \times 100$. The solid dots represent values for partially nephrectomized rats, and the open circles, values for control animals.

error of a single point is 4.5 units parallel to the x axis (urine urea). In other words, half of the values observed lie within 4.5 units of the curve in the x direction. In the direction of the y axis (blood urea) the probable error varies from about 14 units at y equals 100 to 40 units at y equals 300. The scatter of the points around the curve for the animals on M 20 diet is only slightly greater, but for the group on the M 40 diet it is considerably greater. The greatest scatter is seen in the

group on the M 80 diet, in which the probable error of a single point in the x direction is 5 units at the urine urea concentration of 50 and 7.5 units at the value of 20. In the direction of the y axis, the probable error varies from 20 units at y equals 100 to 90 units at y equals 500.

The four unadjusted curves show progressive changes in position. The large number of points defining each curve makes the probable error of the position of each curve very small. The probable error for the animals on the M 10 diet is smallest, and that for the animals on the M 80 diet is largest. The two heavy bars perpendicular to each of the four unadjusted curves give a measure of the accuracy of the position of the curves. The bars extend to three times the probable error on each side of the curve, thus giving odds of 20:1 that the true curve lies within a zone defined by the tips of the bars. Furthermore, the odds are 5:1 that the true curve lies within a zone two-thirds this width. The unadjusted curve for the M 80 data was drawn with strict reference to the regression points, but the position was not correctly represented at the lower end, since there was scarcity of points at y equals 200. The position of the curves at these points for rats on other diets is more accurate. Hence the reliability of the relative positions of the curves cannot be questioned, with the exception of the systematic error noted in the curve for animals with the M 80 diet.

To represent the trend more clearly and to correct for the systematic error of the lower end of the M 80 curve, adjusted curves have been adopted (chart 2), which are probably closer to the true picture. Since the shape of each of the unadjusted curves was practically exponential, the adjusted curves are also exponential, the formulas being given on the chart. The significance of these curves is evident when the values for urea in the blood and in the urine are compared on the same oblique line which represents urea ratios. The absolute amount of urea excreted is related to the degree of renal insufficiency. In animals with normal renal function with ratios of 60, it is seen that the diet has little effect on the urea concentration of the blood and urine. However, when renal function is decreased to a urea ratio of 5, it can be seen that the value for urine urea is increased from 16 to 21 and that the value for the blood urea is increased from 320 to 420 owing to the respective effects of the M 10 and M 80 diets. The differences in the amount of urea excreted by the animals on the various diets at any given urea ratio appear to be significant. Thus it is seen that the dietary regimen is important in its influence on the factors which determine the urea ratio.

The curves in chart 3 represent an analysis of the effect of diet on the concentration of urea in the blood at any given urea ratio in percentage of the mean normal. The exponential equations for the adjusted

curves for urea in the blood and urine were transformed into the equations which gave the relation between the blood urea content and the percentage urea ratio. The curves presented were drawn from these derived formulas. It can be seen that the concentration of blood urea is not affected by diet at any given urea ratio until severe renal insufficiency is encountered. For practical purposes, the differences in

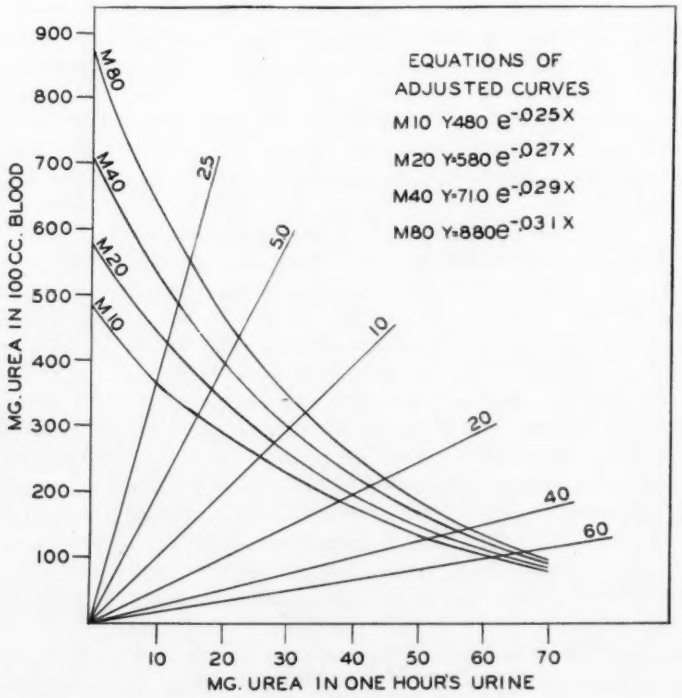

Chart 2.—The relation of the adjusted curves for blood urea and urine urea.

the blood values at any given urea ratio expressed in percentage of the mean normal value are not significant.

MacKay and Rytand [2] expressed the relation of the blood urea concentration to the Addis ratio in patients with Bright's disease in the form of a rectangular hyperbola ($xy = k$). Since similar analyses in partially nephrectomized rats had yielded exponential equations, their

2. MacKay, E. M., and Rytand, D. A.: Significance of the Phenolsulphonphthalein Test of Renal Function, Arch. Int. Med. **55**:131 (Jan.) 1935.

data were recalculated. The values for urea in the urine and blood were obtained from table 3 of MacKay and Rytand's paper, and a mean curve was derived from two regression curves. This curve was readily fitted by an exponential equation, which was transformed into the equation given in chart 3 to express the relation between the concentration of blood urea and the Addis ratio. When the curve corresponding to this equation was drawn on the figure given in MacKay and Rytand's paper, it was found to lie satisfactorily between the two sets

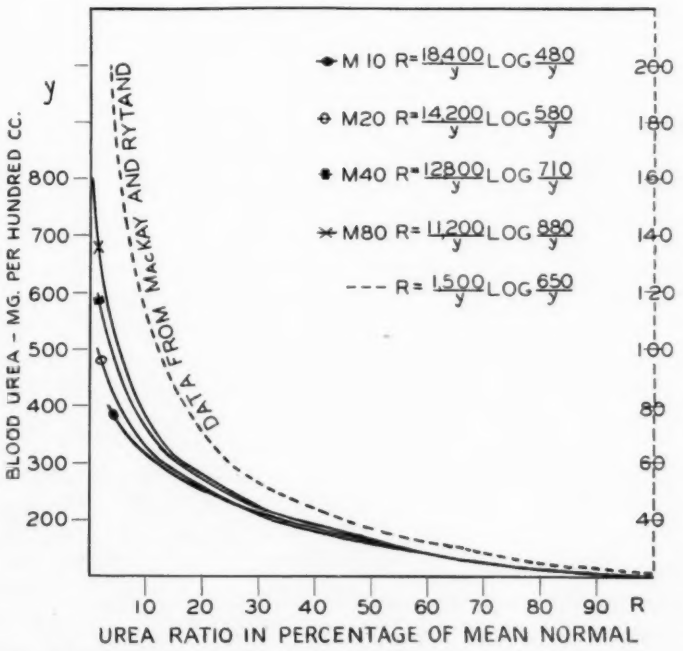

Chart 3.—The relation between the blood urea concentration and the urea ratio in percentage of the mean normal value.

of points computed by these authors, but it did not correspond to the rectangular hyperbola presented. It can be seen in chart 3 that the shape of the curve obtained for nephritic patients is similar to that for experimental animals.

SUMMARY

The effect of diets containing 10, 20, 40 and 80 per cent of whole dried meat on the amount of urea in the blood and urine of rats with

renal function varying from normal to marked renal insufficiency has been investigated. The positions of the exponential curves derived from the data showed that the concentration of urea in the blood and in the urine at any given urea ratio was greater the higher the protein intake. The differences were progressively more marked with increased renal insufficiency.

A comparison of the blood urea concentration and the urea ratio expressed in percentage of the mean normal value indicated that diet has no effect on this relationship until severe renal insufficiency develops.

EXPERIMENTAL RENAL INSUFFICIENCY PRODUCED BY PARTIAL NEPHRECTOMY

VIII. COMPARISON OF THE UREA (ADDIS) RATIO WITH RESULTS OF OTHER TESTS OF RENAL FUNCTION

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AND
STEPHAN LUDEWIG, PH.D.
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Our purpose in this paper is to compare the blood urea concentration and blood pressure and the specific gravity, volume and protein content of urine collected during a concentration test with the urea ratio in partially nephrectomized rats fed diets containing different amounts of whole dried meat. In recent years the urea clearance has been compared with the concentration of urea,[1] and of creatinine [1b] in the blood, hemoglobin content,[1b] phenolsulfonphthalein excretion,[1b, c] urinary specific gravity [2] and $\frac{\text{urea nitrogen}}{\text{nonprotein nitrogen}}$ [3] ratio. In the experiments reported by Addis [4] and Van Slyke [5] the ability of the kidneys to excrete urea appeared to be the most sensitive indicator of the state of renal function.

RESULTS

Blood Urea.—MacKay and MacKay [1a] and Van Slyke and his co-workers [1b] found that the urea concentration of the blood did not rise appreciably until the active kidney tissue was reduced one-half as measured by the urea clearance in patients with Bright's disease. As

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From the Laboratory of Physiological Chemistry, the University of Virginia.
This investigation was made possible by a grant from the National Live Stock and Meat Board and by the Edward N. Gibbs Prize Fund of the New York Academy of Medicine.

1. (*a*) MacKay, E. M., and MacKay, L. L.: J. Clin. Investigation **4**:127, 1927. (*b*) Van Slyke, D. D.; McIntosh, J. F.; Moller, E.; Hannon, R. R., and Johnston, C.: ibid. **8**:357, 1930. (*c*) MacKay, E. M., and Rytand, D. A.: Significance of the Phenolsulphonphthalein Test of Renal Function, Arch. Int. Med. **55**:131 (Jan.) 1935.

2. Alving, A. S., and Van Slyke, D. D.: J. Clin. Investigation **13**:969, 1934.

3. Mosenthal, H. O., and Bruger, M.: The Urea Ratio as a Measure of Renal Function, Arch. Int. Med. **55**:411 (March) 1935.

4. Addis, T.: Am. J. M. Sc. **176**:624, 1928.

5. Van Slyke, D. D.; Stillman, E.; Moller, E.; Ehrich, W.; McIntosh, J. F.; Leiter, L.; MacKay, E. M.; Hannon, R. R.; Moore, N. S., and Johnston, C.: Medicine **9**:257, 1930.

the renal damage progressed from this point, the value for blood urea continued to become elevated. MacKay and Rytand [1c] made a statistical study of the relationship of the concentration of blood urea to renal function in patients with nephritis.

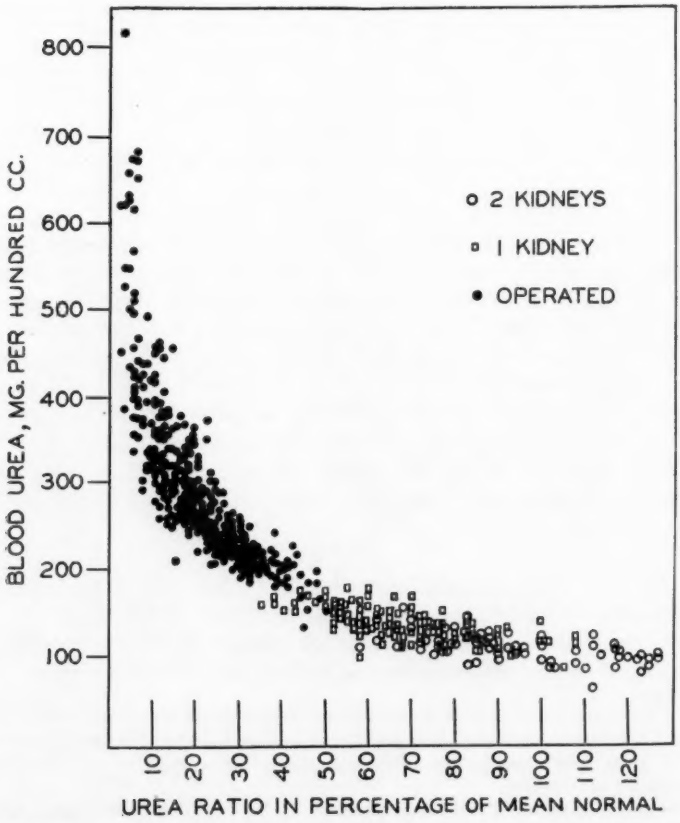

Chart 1.—The relation between the Addis ratio (percentage of normal) and the blood urea concentration.

In chart 1 the scatter point distribution of all values for blood urea and urea ratio in percentage of the mean normal values for all animals is presented. It can be seen that the lower limits for the urea ratio for the unilaterally nephrectomized rats and for the intact rats were about 40 and 60, respectively, and that the highest values for the partially nephrectomized rats were about 50. As the values for the urea ratio

drop below 40 the values for blood urea increase markedly; when the value of 10 is reached the urea concentrations of the blood show a precipitous rise. These results for partially nephrectomized rats confirm reports on nephritic patients by showing that the value for blood urea does not rise until the renal function is reduced one-half and that there is a marked rise in the values for blood urea as the renal damage increases.

Blood Pressure.—Page [6] recently presented evidence to show that high blood pressure is not essential for the maintenance of renal function in patients with chronic Bright's disease.

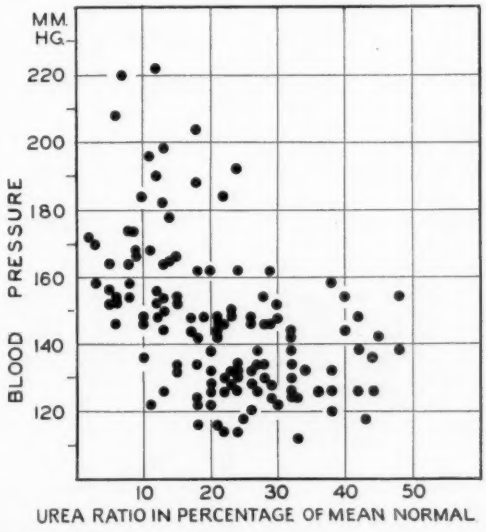

Chart 2.—The relation between the Addis ratio (percentage of normal) and the blood pressure.

The relation between blood pressure and renal function in partially nephrectomized rats is shown in chart 2. All animals having a ratio below 10 have blood pressures above the normal limits (140 mm.), more than half the values being above 160 mm. An appreciable number of animals with a ratio between 10 and 20 have pressures within the normal range, but the majority of them have various degrees of hypertension. The animals with renal function above the percentage urea ratio of 20 show moderate increase in blood pressure in an appreciable number of cases, but most of the values are normal. The variations at any given ratio are large and are not due to dietary differences. Hyperten-

6. Page, I. H.: J. Clin. Investigation **13**:909, 1934.

sion is always encountered in cases of renal insufficiency, but the height of the blood pressure cannot be predicted. There appears to be a compensatory effort to overcome mechanical resistance, at first postulated by Traube,[7] in animals that were fed whole meat and that had lowered renal function.

Urinary Specific Gravity.—Alving and Van Slyke [2] recently published a comprehensive study in which the urea clearance was compared with the specific gravity of urine obtained during concentration tests in persons with nephritis. They concluded that the results of concentration tests are good qualitative indicators of renal function but do not serve to measure the extent of renal damage. It was pointed out that

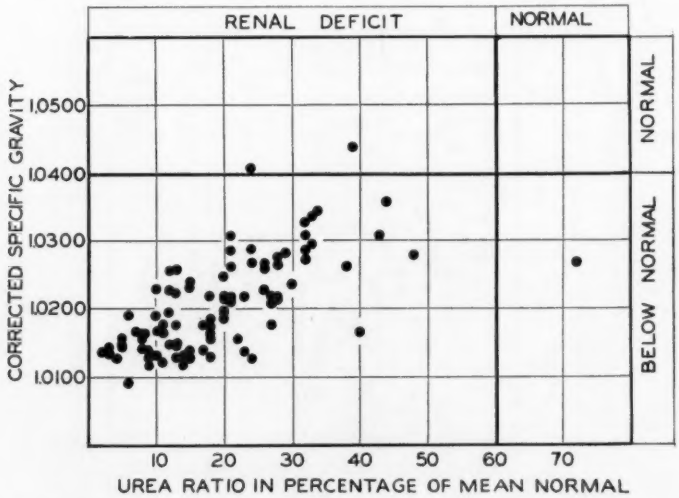

Chart 3.—The relation between the Addis ratio (percentage of normal) and the corrected urinary specific gravity.

the significance of these two tests is different in that the urea clearance test measures the ability to excrete urea and the concentration test measures the ability of the kidney to concentrate mineral salts.

The corrected specific gravities of urine obtained from partially nephrectomized rats during a concentration test were compared with the urea ratio in percentage of the mean normal value in chart 3. No points fall within the normal range. The few specific gravities above the lower

7. Traube, L.: Ueber den Zusammenhang von Herz und Nierenkrankheiten, Berlin, A. Hirschwald, 1856, p. 59.

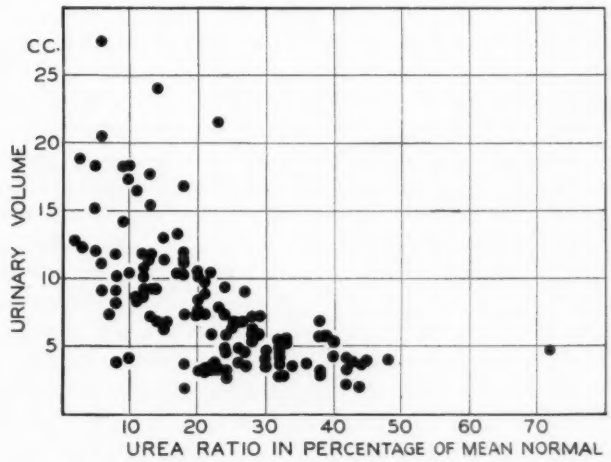

Chart 4.—The relation between the Addis ratio (percentage of normal) and the urinary volume.

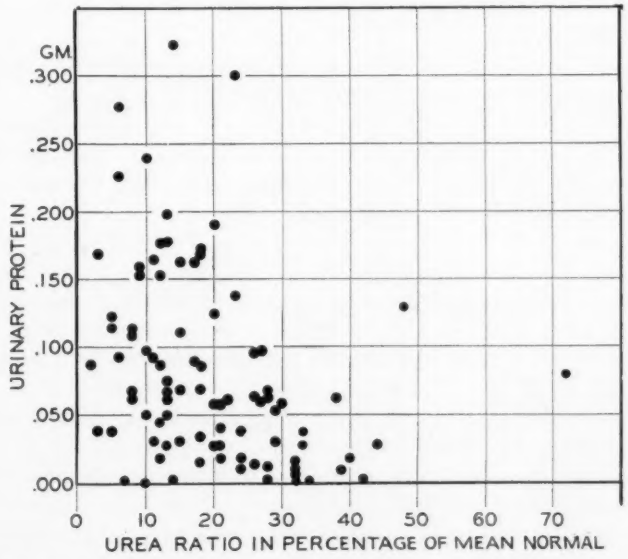

Chart 5.—The relation between the Addis ratio (percentage of normal) and the degree of proteinuria.

limits of normal (1.04) definitely fall in the range of renal insufficiency. Since there is a good correlation between specific gravity and urea ratio, it may be concluded that the specific gravity is a good indicator of renal function.

It was noted that low specific gravity was maintained for a long period in individual animals but that the urea ratio continued to drop during a similar period. An animal may survive for a comparatively long time with this inability to concentrate, but a drop in the urea ratio was invariably soon followed by death. Furthermore, the urea ratio was a better indicator of hypertension than was the specific gravity of the urine. The evidence in this paper is in accord with the statement: "The extent of urine specific gravity fall shows no such uniform relationship to the severity of renal disease as does the urea clearance." [2]

Urinary Volume.—The diagrammatic representation of volume and urea ratio in percentage of mean normal is presented in chart 4. The highest volumes obtained during the concentration test were between the ratio values of 0 and 20. The volumes decreased as renal function increased. The volumes excreted above the percentage ratio of 30 were fairly constant and within the normal range. The urinary output cannot be predicted during a concentration test, since diet determines the excretion of urine at any given urea ratio, particularly in severe renal insufficiency.

Proteinuria.—In chart 5 the amount of protein excreted during the concentration test is compared with the percentage urea ratio. It can be seen that there is no relationship between these two factors. Although the highest output of protein was noted in animals with severe renal insufficiency, the marked variations for any given diet eliminate any conclusion concerning this relationship.

SUMMARY AND CONCLUSIONS

The blood urea and blood pressure and the specific gravity (after correction was made for albumin), volume and protein content of the urine collected during a concentration test were compared with the urea ratio, $\frac{\text{urine excreted per hour}}{\text{urea in 100 cc. blood}}$, in partially nephrectomized rats.

The concentration of urea in the blood after the administration of urea is a good measure of the amount of functioning renal tissue. The most marked variation in the amount of urea in the blood was noted in animals with severe renal insufficiency.

Hypertension of various degrees is encountered in all animals with severe renal insufficiency. An estimation of the degree of renal damage cannot serve as a guide for the prediction of blood pressure.

The specific gravity of the urine serves as a good qualitative test for the detection of damaged renal function.

The urinary volume was extremely variable and was greatest with marked renal damage. There was good correlation between the extent of renal damage and the amount of urine excreted. The excretion of protein was too variable to show any correlation with renal function.

The results obtained for partially nephrectomized animals are similar to those noted for patients suffering from renal insufficiency.

PNEUMONIA DUE TO TYPE I PNEUMOCOCCUS

ANALYSIS OF DEATHS IN CASES IN WHICH SERUM TREATMENT WAS USED

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It has been proved that specific serum definitely reduces the mortality in pneumonia due to type I pneumococcus. This fact has been amply demonstrated by several careful studies [1] on large series of subjects, which, if taken together, total many thousands of patients treated with serum and a comparable number of controls. However, it is disconcerting that in the very reports which are submitted to prove the value of the treatment it is stated that a not inconsiderable number of patients treated with serum succumb in spite of its use. In the series studied by Park and his associates [1a] from the Bellevue, Harlem and New York hospitals, there was a mortality of 19 per cent in the cases in which serum treatment was used, and in the series reported by Cecil and Plummer [1b] there was a mortality of 20.1 per cent.

From 1929 to 1934 we have had under our care one hundred and eighty-five patients with pneumonia due to the type I pneumococcus that were treated with specific serum; forty-four (23.7 per cent) of

From the Department of Medicine, New York University College of Medicine, and the Medical Service of the Third (New York University) Medical Division, Bellevue Hospital.

1. (*a*) Park, W. H.; Bullowa, J. G. M., and Rosenblüth, M. B.: Treatment of Lobar Pneumonia with Refined Specific Antibacterial Serum, J. A. M. A. **91**:1503 (Nov. 17) 1928. (*b*) Cecil, R. L., and Plummer, N.: Pneumococcus Type I Pneumonia, ibid. **95**:1547 (Nov. 22) 1930. (*c*) Cole, Rufus: Serum Treatment in Type I Lobar Pneumonia, ibid. **93**:741 (Sept. 7) 1929. (*d*) Cecil, R. L., and Sutliff, W. D.: Treatment of Lobar Pneumonia with Concentrated Antipneumococcus Serum, ibid. **91**:2035 (Dec. 29) 1928. (*e*) Wadsworth, A. B.: Review of Recently Published Reports on Serum Treatment of Type I Pneumonia, Together with Report of Four Hundred and Forty-Five Additional Cases, Am. J. Hyg. **4**:119 (March) 1924. (*f*) Sutliff, W. D., and Finland, Maxwell: Type I Pneumococcic Infections with Especial Reference to Specific Serum Treatment, New England J. Med. **210**:237 (Feb. 1) 1934. (*g*) Finland, Maxwell: The Serum Treatment of Lobar Pneumonia, ibid. **202**:1244 (June 26) 1930.

the patients died. The purpose of this study was to make a careful inquiry into each of the fatal cases to determine, so far as possible, the factors which contributed to the unfavorable outcome. We believed that a more intensive study of the fatal cases might be fruitful in suggesting improvements in management and that it might supply new evidence for or against the value of serum.

An analysis was made of the following factors, since they seemed the ones most likely to be informative: (1) age; (2) duration of the disease at the time serum treatment was instituted; (3) anoxemia; (4) results of blood culture; (5) amount of serum given; (6) complications and associated diseases, and (7) serum as a cause of death.

FACTORS INFLUENCING MORTALITY RATE

Age.—In table 1 we have shown the age incidence by decades of the patients who recovered and of those who died. It will be noted that whereas no patients in the second decade of life were lost, in 16.6

TABLE 1.—*Age Distribution by Decades of Patients Who Recovered and of Those Who Died*

Age	0-10	10-20	20-30	30-40	40-50	50-60	60-70	70-80
Patients who recovered...	0	5	20	35	51	24	5	1
Patients who died.....	0	0	4	4	11	17	6	2
Total number of patients	0	5	24	39	62	41	11	3
Percentage of mortality	0	0	16.6	10.2	17.7	41.4	54.5	66.6

per cent of those in the third, 10.2 per cent of those in the fourth and 17.7 per cent of those in the fifth the condition terminated fatally. After the age of 50 there was an appreciable rise in the mortality rate, so that among the patients in the sixth decade 41.4 per cent were lost, among those in the seventh 54.5 per cent and among those in the eighth 66.6 per cent. Of the forty-four patients that died, twenty-five were over 50 years of age.

It would appear from these observations that patients over 50 years of age have a severe handicap, based on age alone, in their struggle with this disease.

It is interesting that whereas it is the common impression that infection due to the type I pneumococcus is largely a disease of young people, of our one hundred and eighty-five patients, one hundred and seventeen were over 40 years of age.

Duration of the Disease at the Time Serum Treatment Was Instituted.—It has been shown by several investigators [2] that in patients who

2. Sutliff, W. D., and Finland, M.: Type I Lobar Pneumonia Treated with Concentrated Pneumococcic Antibody (Felton), J. A. M. A. **96**:1465 (May 2) 1931. Footnote 1 *a*, *b*, *d*, *f* and *g*.

are given serum within the first three days of their illness, the results are far better than in those who are treated later.

In table 2 we have shown the period of the disease when serum was first administered to the patients who recovered and to those who died. We have indicated also the percentage of each group whose treatment was begun in each period. The time of onset was fixed by the occurrence of a chill or of thoracic pain, whenever these symptoms were present. In their absence an approximation of the time of the onset was made by determining the period during which the patient was confined to bed with fever and cough. Analysis shows there was an even age distribution in the various categories.

It will be seen, by comparing the time at which treatment was begun (table 2), that of the patients who recovered 49.6 per cent were treated during the first three days and 91.4 per cent during the first week, and of those who died, only 9 per cent were treated during the first three days and only 56.7 per cent during the first week. Conversely, in the

TABLE 2.—*Correlation Between Rate of Mortality and Number of Days After Onset That Serum Treatment Was Instituted*

No. of days after onset that serum therapy was started.....		1–3	3–7	7–14	14+
141 patients who recovered	Number.....	70	59	11	1
	Percentage.....	49.6	41.8	7.8	0.7
44 patients who died	Number.....	4	21	14	5
	Percentage.....	9	47.7	31.80	11.3
Percentage of mortality.....		5.4	26.2	56	83

group that recovered only 8.5 per cent were treated after one week, while in the group that died 42.4 per cent were treated after one week. Only four of the patients who died were treated within three days of the onset. In twenty-one cases a period of from three to seven days elapsed before treatment, and in nineteen cases the period was longer than one week. The delay in treatment was usually due to the patient's late entry into the hospital. In a few cases it was due to difficulties in determining the type of the pneumococcus, either because of absence of sputum, in which case we were forced to await the results of blood culture, or because of an error in the preliminary typing. These difficulties in typing have become infrequent since the introduction of the direct method of Neufeld.

Table 2 shows the correlation between the effectiveness of serum therapy and the stage of the disease at which the treatment was instituted. When therapy was delayed, there was a rapid rise in the rate of mortality. Of the patients treated within the first three days after the onset of the disease, the mortality was 5.4 per cent; of those treated from three to seven days after the onset, the mortality was 26.2 per

cent; of those treated from seven to fourteen days after the onset, the mortality was 56 per cent, and of those treated fourteen days or later after the onset, the mortality was 83 per cent.

Anoxemia.—The relation of anoxemia to fatal outcome was studied in all cases by carefully noting the presence or absence of the clinical signs of anoxemia and in fifteen of the cases also by determining the oxygen saturation of the arterial blood. Some clinical signs, especially cyanosis, tachypnea, tachycardia, nervous irritability, delirium and somnolence, were present in every case. In a small number of cases the anoxemia not only was present but was the outstanding clinical feature. Cyanosis, which in the average case was limited to a faintly blue tinge in the beds of the finger-nails, in the cases of more severe involvement was darker and was readily apparent not only in the beds of the finger-nails but in the mucous membranes and in the skin. A report of one such case follows:

CASE 43.—J. D., a man 38 years of age, was admitted to the hospital on the third day of illness. The sputum showed the type I pneumococcus. The blood culture was negative. Serum therapy was started early, and 800,000 units was given in all. Cyanosis, noted from the beginning, became gradually more intense. Jaundice was present. The icterus index was 65. Two subsequent blood cultures were negative, and the blood showed a 4 plus reaction for type I agglutinins.

On the sixth day an analysis of the gases in the arterial blood showed the oxygen saturation to be 86 per cent. On the seventh day the oxygen saturation was 85 per cent, and on the eighth day, 82.5 per cent. On the ninth day the patient appeared to be dying. The respiratory rate was 40, and the pulse rate was 130. He was comatose, deeply jaundiced and extremely cyanotic. On the twelfth day the oxygen saturation was 79.7 per cent. He died on the thirteenth day. Postmortem examination showed the presence of lobar pneumonia, fibrinous pleurisy and bilateral hydrothorax. When a section of the lung was made, pus exuded from the bronchi. Microscopic examination of the kidneys showed acute interstitial nephritis.

This case is of particular interest because it gives a clue to the mechanism causing death in certain cases of pneumonia. As will be pointed out later, in 79 per cent of the fatal cases the condition was associated with bacteremia, and death in these cases was commonly caused by some septic complication. In case 43 several blood cultures were made, but at no time was bacteremia demonstrated. The entire clinical picture was dominated by the signs of lack of oxygen. Not only was there cyanosis, which from day to day became deeper, but an examination of the arterial blood showed a progressive lowering of oxygen saturation from 86.3 per cent on the fifth day after admission to 79.7 per cent on the twelfth day. The explanation suggested by these facts, in addition to the postmortem observations, was that the profuse purulent secretion in the bronchial tree acted as an effective barrier against the interchange of gas and caused death by asphyxia.

In the following case the patient presented a similar clinical picture of progressive anoxemia with absence of bacteremia:

CASE 12.—S. B., a man 56 years of age, was admitted to the hospital on the fourth day of illness. There was consolidation of the upper lobe of the right lung. On the day of his admission a deep cyanosis was observed. The sputum showed the type I pneumococcus. The blood culture was negative. He was given 250,000 units of type I serum. Two subsequent blood cultures were negative. His course was rapidly downhill, with cyanosis continuing as the outstanding feature. The patient died four days after admission. Postmortem examination showed the presence of lobar pneumonia, acute fibrinous pleuritis, acute purulent bronchitis and tracheitis; atheromatous changes of the aortic valve, aorta and coronary arteries; nephrosclerosis, and congestion of the brain.

This case in its essential features bears a striking resemblance to case 43. At no time was bacteremia demonstrated, even though blood

TABLE 3.—*Percentage of Oxygen Saturation in Fifteen Cases*

Case No.	Percentage of Oxygen Saturation
1	75–82
2	70.4–87.2
13	90.4
14	82.7
15	81.6–84
16	75.1
17	86.3–91.6
18	88.0
19	76.8
20	91.6
21	85.5
22	76.8–93.5
23	93.2
24	61.4
25	88.7

cultures were made on three occasions. The clinical picture was dominated by signs of profound anoxemia, so that even on the first day in the hospital deep cyanosis was present. The mechanism of this lack of oxygen was apparent at autopsy when it was noted that the trachea and bronchi were the seat of an extensive inflammation and that their lumens were filled with a seropurulent exudate. In this case, as in the previous one, it seems probable that the cause of death was asphyxia.

In several other cases anoxemia appeared to play a considerable part in the picture of the disease, but because there was a concurrent septicemia it was difficult to estimate clearly its significance. The fifteen cases in which the oxygen saturation was determined were proof of how frequently a severe anoxemia was present. The figures are given in table 3. In only one of the fifteen cases was a value (93.2 per cent) approaching the normal level found, and in only three was the figure above 90 per cent. In six cases the oxygen saturation was between 80 and 90 per cent, in five cases between 70 and 80 per cent and in one case between 60 and 70 per cent. These fifteen cases may

be regarded as reasonably representative of the entire group, since they were not selected but were taken at random during one period of the study.

Bacteremia.—Blood for culture was taken from all patients soon after admission. No serum was given until this had been done. If the culture was positive, additional cultures were made daily or every second day. If the culture was negative, only one or two additional cultures were made during the period of the administration of the serum, unless there was some specific indication, such as the occurrence of a chill, of a sharp rise in temperature or of a complication. In several cases only one culture was made because the patient died before further study was possible. In twenty-four of the cases in which the blood yielded the organisms on culture the number of colonies per cubic centimeter

TABLE 4.—*Distribution of Cases According to Number of Colonies per Cubic Centimeter of Blood*

No. of Colonies per Cc. of Blood	No. of Cases
1– 10	3
10– 25	4
25– 50	2
50–100	3
100–200	2
200–500	3
500–1,000	4
Over 1,000	3

of blood was counted. In one case, through inadvertence, no culture was made.

No other finding was so striking as the frequency and the severity of bacteremia. It was present in thirty-four, or 79 per cent, of the forty-three cases in which blood cultures were made. In thirty-two of the cases the bacteremia was demonstrated in the first culture, that is, in the blood taken before the administration of serum. In many of these cases an overwhelming bacteremia was already present. This condition is best shown in table 4, in which the twenty-four cases in which the number of colonies per cubic centimeter of blood was determined are grouped according to the number of colonies found. The actual colony counts are given in table 9.

In twenty-six cases one or more cultures were made subsequent to the institution of serum therapy. In eleven of these cases the culture was negative although prior to the administration of serum a culture had been positive. In table 5 we have grouped these cases and also have recorded the dose of serum required to sterilize the blood stream. Several cases are especially noteworthy because of the severity of the bacteremia.

In case 19, in which there were over 1,000 colonies per cubic centimeter of blood, the culture became negative after the administration of 360,500 units of serum. In case 36, in which there were over 1,000 colonies per cubic centimeter, the culture became negative after 200,000 units; in case 1 in which there were over 500 colonies, the culture became negative after 200,000 units; in case 6, in which there were over 300 colonies, the culture became negative after 20,000 units; in case 14, in which there were 271 colonies, the culture became negative after 356,000 units, and in case 15, in which there were 107 colonies, the culture became negative after 350,000 units. In several cases, although the bacteremia did not clear up entirely after the administration of serum, there was a decided reduction in the number of colonies.

Absence of Bacteremia in Fatal Cases.—As we have shown, most patients with pneumonia who die have sepsis, with or without some

TABLE 5.—*Cases in Which the Blood Culture Was Positive Before and Negative After the Administration of Serum*

Case No.	No. of Colonies per Cc. of Blood	Dose of Serum After Which Blood Culture Became Negative, Units
19	Over 1,000	360,500
37	Over 1,000	200,000
1	Over 500	200,000
6	Over 300	30,000
14	271	356,000
15	107	350,000
17	66	260,000
2	50	219,500
8	41	400,000
11	16	70,000
9	1	130,000

complication dependent on it. However, there were in our series of fatal cases eight in which, in spite of repeated blood cultures, no bacteremia was demonstrable. A close scrutiny of these cases seemed desirable in order to determine, if possible, the cause of death. Two cases (12 and 14) have already been described, and it was shown that in both death appeared to be caused by an intense anoxemia. In three other cases (10, 28 and 29) the clinical picture presented by the patient was dominated throughout by the signs of lack of oxygen, but since no postmortem examination was made, we cannot offer any certain explanation of the cause of death.

In the three cases reports of which follow neither bacteremia nor severe anoxemia was observed.

CASE 29.—F. M., a man 25 years of age, was discharged from the hospital with the diagnosis of acute bronchitis and toxic dermatitis. In seven days he was readmitted, twenty-four hours after the occurrence of a chill. Two days later signs of consolidation were observed over the lower lobe of the left lung. The sputum showed the type I pneumococcus. The blood culture was negative. Tests

of the skin and eyes gave negative results. The patient was given 300,000 units of type I serum. After the treatment there were defervescence and definite general improvement. On the sixth day after the institution of serum therapy there was a sharp rise in temperature to 104 F., and generalized lymphadenopathy, pains in the joints and urticaria were noted. The symptoms of serum sickness persisted for four days; then there was a further rise in temperature, to 106.2 F., and the patient died suddenly. There was no autopsy.

No certain explanation of the events in this case is offered, but the fact that death occurred suddenly while the patient was in the midst of a severe attack of serum sickness makes it seem possible that death was related to the reaction to the serum.

Case 25.—T. G., a man 70 years of age, was admitted to the service for patients with cardiac disease, with a diagnosis of arteriosclerotic heart disease, rapid auricular fibrillation and heart failure. With rest in bed he improved but was still dyspneic and orthopneic. There was only slight loss of weight. The ventricular rate was 134, with a pulse deficit of 22. The fibrillation persisted. Six days after admission the temperature rose to 104 F., and signs of pneumonia of the upper lobe of the left lung were noted. He was then given digitalis, receiving 36 cat units in a period of four days, but it had little effect on the ventricular rate or on the pulse deficit. He was also given 210,000 units of type I antipneumococcus serum. The blood cultures, taken during the febrile period, were negative. The oxygen saturation of the arterial blood on the day before death was 88.4 per cent. He died ten days after admission, which was four days after the development of the pneumonia. There was no autopsy.

We feel that the pneumonia in this case, occurring as an intercurrent infection in the course of cardiac failure, was of less importance than the heart failure in causing the patient's death.

Case 34.—A. P., a white man aged 43, was admitted to the hospital on the fourth day of illness, with consolidation of the lower lobe of the left lung. There were pain and severe tenderness in the left costovertebral angle and in the left side of the abdomen. A difference of opinion arose as to the condition of the heart; one observer reported that there was no disease, while another thought that there was a chronic cardiac lesion involving the mitral and aortic valves. The urine showed a heavy reaction for albumin and clumps of leukocytes. The blood cultures were negative. He was given 500,000 units of serum. Pulmonary edema developed, and he died four days after the onset. There was no autopsy.

The cause of death in this case is uncertain. Heart disease may have been a factor. The possibility of an acute infection of the kidneys was also considered, because of the costovertebral pain, the tenderness and the pus in the urine. In the absence of a postmortem examination, no definite diagnosis could be made.

An analysis of the eight cases in which there was no bacteremia shows that in five there was profound anoxemia resulting from various causes. One patient died during a severe attack of serum sickness; another had congestive heart failure before the onset of the pneumonia and throughout its course. In the eighth case the cause of death was problematic.

Dosage of Serum.—A question of major importance was whether the dose of serum had been adequate. Dosage is one factor that can be modified should our experience show that this is necessary.

While we have at no time had an inflexible rule as to the amount of serum to be given, the suggested dose was 10,000 units as soon as the disease was determined to be due to the type I pneumococcus, and succeeding doses of 20,000 units at intervals which varied from two to four hours; thus the total dose for the first day was at least 100,000 units. For a patient with a positive blood culture this dose was doubled. If we arbitrarily assume that even so small a dose as 80,000 units of serum might reasonably be regarded as sufficient, we are forced to admit that eleven of our forty-four patients were inadequately treated. We reviewed the eleven cases to determine why the dose of serum was so small; the explanation for each instance is given in table 6. From this table it can be seen that the two most common reasons for an inadequate dose of serum were a delay in typing and sensitiveness to serum.

TABLE 6.—*Cases in Which the Patient Received Insufficient Serum and the Explanation for the Inadequate Treatment*

Case No.	Name	Dose, Units	Explanation
4	J. W.	72,000	Error in preliminary typing
5	C. F.	20,000	Delay in typing
8	N. O.	60,000	Delay in diagnosis
11	P. S.	70,000	Sudden death of patient from embolism of popliteal artery
13	C. F.	22,000	Sudden death of patient one hour after first dose of serum was administered
18	J. S.	20,000	Delay in typing
23	J. D.	1,000	Patient died during administration of serum
26	E. A.	40,000	Delay in typing
38	R. M.	60,000	Patient's late entry into hospital
42	P. T.	40,000	Delay in typing, because of absence of sputum
43	A. M.	1,000	Serum discontinued because of anaphylactoid reaction

Complications and Associated Diseases.—We have regarded as complications only those conditions that were directly attributable to the pneumococcic infection and the presence of which was proved either at autopsy or by some clinical procedure, such as a spinal tap or thoracentesis. Many other conditions which were found to coexist but which were not caused by the infection have been grouped separately as associated diseases.

The most frequent complications were meningitis (in seven cases), empyema (in six cases) and bacterial endocarditis (in four cases). These and other less frequent complications are listed in table 7. All the complications, except those in the lung itself or in the pleura, appeared to be due to a localization of the organisms from septicemia. Not infrequently the complication was discovered at a time when the blood culture was sterile, but in every case a preceding bacteremia had been demonstrated. In five cases (1, 2, 3, 15, 19) the blood culture had been positive, but was negative following the institution of serum therapy, but not before the infection had localized and formed another focus.

To review: The reason for the failure of serum therapy in these cases is shown. For instance, in case 1, in which there were over 500 colonies per cubic centimeter of blood, the culture became negative after the administration of 200,000 units of serum. However, the uselessness of sterilizing the blood stream became apparent when we observed at postmortem examination that the patient had not only the pneumonia, empyema and purulent arthritis but also bacterial endocarditis with large vegetations on the tricuspid and mitral valves. In case 19, in which there were over 1,000 colonies per cubic centimeter of blood, the blood

TABLE 7.—*Frequency of Complications*

	No. of Cases
Purulent meningitis	7
Empyema	6
Acute bacterial endocarditis	4
Purulent pericarditis	3
Purulent bursitis	3
Pleural effusion	2
Pulmonary abscess	2
Acute diffuse glomerular nephritis	1
Acute interstitial nephritis	1
Multiple abscesses of kidney	2
Panophthalmitis	1

TABLE 8.—*Frequency of Associated Conditions in Fatal Cases*

	No. of Cases
Coronary disease	5
Nephrosclerosis	5
Chronic valvular heart disease	3
Chronic pulmonary tuberculosis	4
Emphysema	2
Cholecystitis	2
Cholelithiasis	1
Syphilis	2
Embolism of popliteal artery	1
Thrombosis of external iliac artery	1
Sclerosis of the aorta	1
Pyelitis	1
Bronchiectasis	1
Chronic leptomeningitis	1

was sterilized, but the infection had already localized on the meninges. In case 15, in which there were 107 colonies per cubic centimeter of blood, although the culture became sterile, at autopsy the presence of meningitis and endocarditis was observed. In case 3, in which there were 41 colonies per cubic centimeter of blood, the culture became sterile, but the presence of meningitis was noted at autopsy.

Cases such as these are not evidence against the value of serum. They do, however, bear witness to the importance of instituting serum therapy at the earliest possible moment. Once the bacteremia has localized in a vital structure, no amount of serum will be of avail, and an increase in the dose cannot compensate for a delay in administering it.

In table 8 the associated diseases are recorded. They occurred mainly in the older patients and consisted in large part of cardiovascular con-

TABLE 9.—*Analysis of Forty-Four Fatal Cases of Pneumonia Due to the Type I Pneumococcus in Which the Patient Was Treated with Serum*

Case No.	Name	Age	Sex	Oxygen Saturation, %	Use of Alcohol*	Duration of Illness to First Dose of Serum, Days	Blood Culture Before Serum	Total Dose of Serum, Units	Blood Culture After Serum Therapy	Complications	Autopsy†
1	H. G.	41	M	75-82	++++	25	Positive, 500+ colonies	650,000	Negative after 200,000 units	Endocarditis; pericarditis; empyema; arthritis	Lobar pneumonia R.L.L., L.L.L., and R.M.L.; empyema; purulent pericarditis; acute endocarditis with vegetations on tricuspid and mitral valves
2	R. S.	36	M	70.4-87.2	++	8	Positive, 50+ colonies	361,500	Negative after 219,500 units	Empyema; arthritis	Lobar pneumonia of right lung; empyema; brown atrophy of heart
3	B. H.	22	M	.....	.....	5	Positive, 41 colonies	400,000	Negative	Meningitis; pericarditis	Purulent (pneumococcus type I) meningitis; hemohydrothorax; fibrinous pleuritis; lobar pneumonia; serous pericarditis on left
4	J. W.	49	M	.....	++++	6	Negative	72,000	Positive, 60 colonies	.....	Lobar pneumonia L.L.L. and R.U.L.; coronary sclerosis; nephrosclerosis
5	C. F.	57	M	.....	+++	4	Positive, 500+ colonies	20,000	Not taken	.....	Lobar pneumonia L.L.L.; chronic mitral and aortic valvular heart disease; pulmonary edema; nephrosclerosis; suppurative pleuritis
6	W. S.	57	M	.....	++++	8	Positive, 300+ colonies	205,000	Negative after 20,000 units	.....	Lobar pneumonia left as. of aortic valve
7	S. S.	24	M	.....	No	5	Positive, 19 colonies	80,000	Negative after 20,000 units	.....	
8	N. O.	45	M	.....	No	7	Positive, 500+ colonies	60,000	Positive, 125 colonies	Cholecystitis; cholelithiasis; fibrinopurulent pleuritis	Lobar pneumonia; healed pulmonary tuberculosis; chronic cholecystitis
9	I. D.	47	M	.....	+++	23	Positive, 1 colony of pneumococci and 16 of hemolytic streptococci	130,000	Negative for pneumococci, positive for hemolytic streptococci	Pulmonary tuberculosis; syphilis	Chronic ulcerative tuberculosis; lobar pneumonia L.L.L.; serous pleural effusion; cardiac hypertrophy
10	V. G.	38	M	.....	++	8	Negative	190,000	Negative	Jaundice	
11	P. S.	58	M	.....	No	9	Positive, 16 colonies	70,000	Negative	Embolism of popliteal artery	
12	S. P.	56	M	.....	No	4	Negative	250,000	Negative	None	Emaciation; lobar pneumonia R.U.L.; sclerosis of aortic valve; sclerosis of

12	S. B.	56	M	.....	No	4	Negative	250,000	Negative	None	Emaciation; lobar pneumonia R.U.L.; sclerosis of aortic valve; sclerosis of aorta; nephrosclerosis
13	R. S.	30	M	90.4	No	11	Positive, 2 colonies	22,000	Not done	Anaphylactoid reaction	
14	W. G.	63	M	82.7	++	8	Positive, 271 colonies	356,000	Negative	Azotemia	
15	W. M.	48	M	81.6-84	+++	5	Positive, 107 colonies	350,000	Negative; later positive	Pericarditis; endocarditis; meningitis; pulmonary abscess	Lobar pneumonia left lung; pulmonary abscess; acute endocarditis with vegetations of mitral and aortic valves; acute diffuse glomerular nephritis; focal renal abscesses; purulent meningitis; endocarditis of right auricle
16	F. H.	55	M	75.1	++++	21	Positive, 500 colonies	85,200	Not done	None	
17	T. H.	52	M	86.3-91.6	++	2	Positive, 66 colonies	260,000	Negative	None	
18	J. S.	47	M	88.0	No	4	Positive, 1,000 colonies	20 cc.	Not done; patient died	Meningitis	Lobar pneumonia R.L.L.; spinal fluid cloudy; pure culture of type I pneumococcus
19	C. R.	43	M	76.8	No	9	Positive, 1,000 colonies	360,500	Negative	Meningitis (proved by tap)	
20	J. Y.	50	M	91.6	++++	5	Negative	480,000	Positive, 300 colonies	Meningitis (proved by tap)	
21	J. C.	50	M	85.5-87	++++	18	Positive, 20 colonies	290,000	Positive, 109 colonies —pneumococci, also Friedländer bacilli	None	Lobar pneumonia of right lung; pulmonary tuberculosis; healed fragmentation of heart muscles on left
22	W. H.	42	M	76.8-93.5	++++	16	Positive, 200 colonies	290,000	Positive, 4 colonies	None	
23	J. D.	29	M	92.2	++++	2	Positive, 1,000 colonies	Only a few cc.	Not done	Anaphylactoid reaction	
24	M. S.	69	M	61.4	++++	6	Positive, 6 colonies	112,000	Not done	None	
25	T. G.	70	M	88.4	++++	3	Negative	210,000	Negative	Heart failure	
26	E. A.	65	F	.....	++++	6	Positive	40,000	Negative	Auricular fibrillation	
27	H. K.	50	M	.....	++	8	Negative	80,000	Not done	None	
28	R. S.	50	F	.....	+++	8	Negative	140,000	Not done	Cyanosis ++++	
29	E. M.	25	M	.....	No	12	Negative	300,000	Not done	Serum sickness	
30	U. G.	53	M	.....	++++	10	Positive	80,000	Not done; patient died	Acute bacterial endocarditis	Lobar pneumonia R.U.L. and R.M.L.; pleural effusion; acute endocarditis with vegetations on mitral and aortic valves; pulmonary edema
31	W.	44	M	.....	.....	4	Positive	720,000	Positive	.....	
32	J. P.	67	M	.....	No	14	Positive	200,000	.....	None	

TABLE 9.—*Analysis of Forty-Four Fatal Cases of Pneumonia Due to the Type I Pneumococcus in Which the Patient Was Treated with Serum—Continued*

Case No.	Name	Age	Sex	Oxygen Saturation, %	Use of Alcohol*	Duration of Illness to First Dose of Serum, Days	Blood Culture Before Serum	Total Dose of Serum, Units	Blood Culture After Serum Therapy	Complications	Autopsy†
33	E. D.	50	M	.....	No	8	Negative	80,000	.....	Syphilis	Lobar pneumonia L.U.L., L.L.L., and R.L.L.; coronary sclerosis; thrombus of exterior iliac artery; chronic leptomeningitis
34	A. P.	43	M	.....	+++	4	Negative	500,000	.....	Pyelitis	
35	G. P.	62	M	.....	++++	14	Positive	200,000	None	Empyema	Lobar pneumonia R.L.L.; empyema (right); pulmonary edema; cardiac hypertrophy and dilatation; coronary sclerosis; emphysema; bronchiectasis
36	H. M.	51	M	.....	++++	7	Positive, 1,000 colonies	200,000	Negative	None	
37	R. M.	51	M	.....	++++	6	Positive	60,000	Not taken; patient died	.....	Cholecystitis; lobar pneumonia R.L.U. and R.M.L.
38	A. K.	56	M	.....	++	7	Positive, 40 colonies	160,000	.....	.....	
39	H. S.	55	M	.....	+++	6	Positive	500,000	Negative	.....	
40	W. L.	66	M	.....	+++	4	Positive	400,000	Positive, innumerable colonies	Panophthalmitis; pneumococcic arthritis; pneumococcic meningitis	Lobar pneumonia; multiple abscesses R.U.L. and R.M.L.; acute purulent arthritis; acute ophthalmitis; empyema on left; coronary sclerosis on right
41	P. T.	56	M	.....	+++	7	Not done; no record	40,000; patient died	Not done; no record	.....	Lobar pneumonia R.U.L.; healed bilateral apical tuberculosis; fibrosis of myocardium; renal sclerosis
42	A. M.	47	M	.....	+++	4	Positive, 51 colonies	1,000	Positive	.....	
43	J. D.	38	M	.....	++	3	Negative	800,000	Negative	Jaundice	Lobar pneumonia right lung; hydrothorax; acute interstitial nephritis; cardiac hypertrophy; mild coronary sclerosis
44	S. P.	72	M	.....	No	7	Positive, 10 colonies	1,160,000	Positive, 18 colonies	Meningitis; endocarditis	Lobar pneumonia R.L.L. and L.L.L.; emphysema; acute vegetative and ulcerative endocarditis

* The number of plus signs indicates the degree to which alcohol had been used: +, occasional use; ++, moderate use; +++, heavy use; ++++, habitual excessive use.

† The abbreviations are: R.L.L., the lower lobe of the right lung; L.L.L., the lower lobe of the left lung; R.M.L., the middle lobe of the right lung, and L.U.L., the upper lobe of the left lung.

ditions, such as coronary disease, nephrosclerosis, chronic valvular heart disease and arteriosclerosis. The higher mortality rate in the advanced age group is probably dependent to some extent on the presence of associated conditions.

Deaths Due to Serum.—In a study of this kind, the question presents itself as to whether some of the deaths occurred not in spite of serum treatment but because of it. In only three of the cases did this possibility seem worthy of consideration: In case 23 (J. D., aged 29) the blood culture showed over 1,000 colonies per cubic centimeter. Tests of the skin and eyes gave negative results. During the administration of the first dose of serum, the patient became dyspneic and rigid; he blanched and died within a few minutes, in spite of repeated injections of epinephrine hydrochloride.

In case 13 (R. S., aged 30) the blood yielded the organisms on culture. Tests of the skin and eyes gave negative results. He was given intravenously 11 cc. of serum containing 22,000 units. No reaction was noted until one hour after the injection, when he became agitated and cyanotic and gasped for breath. There was bleeding from the gums. He was given epinephrine repeatedly. The condition persisted for one hour and a half, and the patient died.

The third case (29) has already been described. The patient died during serum sickness; the fact that a possible relationship existed between the serum therapy and death was pointed out. In the first two cases the relationship between the serum and the fatality seemed to be reasonably clear. It is worthy of note that the reactions occurred despite the fact that tests of the skin and eyes of the patients gave negative results.

SUMMARY

An analysis of forty-four fatal cases of pneumonia due to the type I pneumococcus in which serum treatment was instituted showed that:

1. The majority of patients were over 50 years of age.

2. Almost invariably serum treatment had been started late.

3. Only 9 per cent of the patients who died were treated within the first three days, in contrast to 49.6 per cent of those who recovered.

4. The mortality among 74 patients whose treatment was started during the first three days after onset was 5.4 per cent; among 80 patients treated between three and seven days after the onset, 26 per cent, and among 25 patients treated between seven and fourteen days after the onset, 56 per cent.

5. Some degree of anoxemia was present in every case. In ten, the anoxemia was so severe as to be a dominant feature.

6. In thirty-four, or 79 per cent, of the cases bacteremia was demonstrated.

7. In many of the cases in which bacteremia was observed, the blood culture was sterile after the institution of serum therapy; in others the number of colonies was reduced.

8. Eleven patients received an inadequate amount of serum, for the various reasons specified.

9. Complications were frequent, especially those caused by hematogenous spread, such as meningitis and endocarditis.

10. The number of conditions associated with the disease, especially in the older patients, perhaps contributed to the higher mortality rate among them.

EFFECT OF FEEDING OF THYROID OR SALT AND OF THYROIDECTOMY ON FLUID EXCHANGE OF CATS WITH DIABETES INSIPIDUS

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A marked and permanent increase in the water exchange of the body, which we believe represents true diabetes insipidus, is caused in cats and monkeys by lesions in the hypothalamus which interrupt bilaterally the supra-optico-hypophyseal tracts. The autopsy picture in these animals has shown degeneration of these tracts in the pituitary stalk and a disappearance of the plexus formed by their fibers in the pars nervosa of the hypophysis. Atrophy of the supra-optic nuclei and of the posterior lobe is always associated with degeneration of the supra-optico-hypophyseal tract (Fisher, Ingram and Ranson;[1] Fisher, Ingram, Hare and Ranson;[2] Ingram, Fisher and Ranson[3]).

While the cats with experimental diabetes insipidus were under observation, experiments were conducted to determine the relation of the thyroid gland to the polyuria by removing the gland in three cats and by feeding thyroid to a considerably larger number. The effect on the water exchange of feeding fairly large quantities of sodium chloride was also studied. The results obtained in these experiments are of some interest in relation to the difficult problem of the etiology of diabetes insipidus, and they throw light on the mechanism of the regulation of water metabolism generally.

METHODS

The mode of production, development and course of diabetes insipidus in a number of the animals used in this investigation have been reported in another article (Fisher, Ingram and Ranson[1]). The operative procedure and the aftercare of the additional animals used were the same as those previously described.

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1. Fisher, C.; Ingram, W. R., and Ranson, S. W.: Relation of Hypothalamico-hypophyseal System to Diabetes Insipidus, Arch. Neurol. & Psychiat. **34**:124 (July) 1935.

2. Fisher, C.; Ingram, W. R.; Hare, W. K., and Ranson, S. W.: The Degeneration of the Supra-Optico-Hypophyseal System in Diabetes Insipidus, Anat. Rec. **63**:29, 1935.

3. Ingram, W. R.; Fisher, C., and Ranson, S. W.: Experimental Diabetes Insipidus in the Monkey, Arch. Int. Med. **57**:1067 (June) 1936.

The cats were kept on a constant daily diet of 60 Gm. of ground beef hearts and 100 cc. of milk and were given a measured excess of water each day. The thyroid [4] and sodium chloride were administered by mixing them with the ground beef hearts. The following animals, fifteen in all, were fed varying doses of thyroid for varying periods:

Two cats with marked permanent polyuria (166 and D 16)

Two cats with moderate permanent polyuria (125 and 168)

Two thyroidectomized cats with marked permanent polyuria (91 and D 5)

Two cats with moderate polyuria which had diminished so that the excretion was approximately normal at the time the thyroid was fed (D 6 and D 18)

Two cats which had undergone subtotal removal of the neuro-intermediate lobe of the hypophysis (H 1 and H 2). The anatomic observations on these two animals have been reported in another article (Fisher, Ingram, Hare and Ranson [2]). Neither of these cats showed permanent polyuria following operation.

Five normal cats (T 1, L 1, L 4, L 5 and N 46)

The fourteen cats which were fed salt may be divided into the following groups:

Two cats with marked permanent polyuria (91 and D 32)

One cat with moderate permanent polyuria (125)

Two cats with moderate polyuria which had diminished so that the excretion was approximately normal at the time the salt was fed (D 6 and D 18)

Two cats which had undergone subtotal removal of the neuro-intermediate lobe of the hypophysis (H 1 and H 2)

Seven normal cats (L 1, L 2, L 4, T 1, N 7, N 8 and N 10)

Bilateral thyroidectomy was performed on three animals with marked permanent polyuria: in cat 91 after diabetes insipidus had been present for about five months and in cats D 5 and D 9 two months after the onset of permanent polyuria. The operations were performed under aseptic conditions, and the removed thyroid glands were preserved in solution of formaldehyde, sectioned, and stained with hematoxylin and eosin in order to check the completeness of the removal. These three cats were kept on the same diet after operation as before, and careful records were made of the fluid exchange in order to determine whether the thyroidectomy had any influence on it.

RESULTS IN NORMAL CATS

Effect of Thyroid.—The five normal animals (table 1) showed only slight increases in the water exchange after being fed large doses of thyroid continuously for several weeks. The most marked increase in the output of urine was noted in cat L 1. The successive columns in table 1, from left to right, indicate that this cat was fed 1 Gm. of thyroid daily for eight days, 2 Gm. daily during the next five days and 3 Gm. during the last five days. The output of urine averaged 104 cc. during the four days immediately preceding the feeding of thyroid and the intake of 100 cc. of milk, no water being drunk. During the period in which thyroid was given the water exchange was slightly lower than normal, but during the eight days following cessation of the administration of thyroid the output of urine and the intake of fluid increased to an average of 130 cc. daily, the greatest output of urine being 220 cc. and the greatest intake of fluid being 175 cc. on the eighth postfeeding day. The average output of urine and the greatest water exchange in the other normal cats during the period following the cessation of the thyroid feeding were less than in the case of cat L 1, even though larger doses were given. However, in both cat T 1 and cat

4. Armour's thyroid was used in this work.

TABLE 1.—*The Effect of the Feeding of Thyroid on the Water Exchange of Normal Cats and of Cats with Injury to the Supra-Optico-Hypophyseal System*

TABLE 1.—*The Effect of the Feeding of Thyroid on the Water Exchange of Normal Cats and of Cats with Injury to the Supra-Optico-Hypophyseal System*

Cat No.	Dose		Water Exchange Before Feeding			Water Exchange During Feeding		Water Exchange After Feeding			Peak of Water Exchange		Time When Peak Occurred	
	Gm.	Time, Days	Average Amount of Urine, Cc.	Average Amount of Fluid, Cc.	Time, Days	Average Amount of Urine, Cc.	Average Amount of Fluid, Cc.	Average Amount of Urine, Cc.	Average Amount of Fluid, Cc.	Time, Days	Average Amount of Urine, Cc.	Average Amount of Fluid, Cc.	Urine	Fluid
Normal cats														
T1	1	8	98	100	3	109	100							
	2	9	...	...	.	108	111							
	3	8	...	...	.	116	138							
	4	4	...	...	.	110	142	74	113	7	160	165	5th day on 1 Gm.	6th day on 3 Gm.
L1	1	8	104	100	4	92	100							
	2	5	...	...	.	92	104							
	3	5	...	...	.	84	100	130	130	8	220	175	8th postfeeding day	8th postfeeding day
L4	1	8	82	100	3	75	94							
	2	5	...	...	.	102	106							
	3	5	...	...	.	129	121							
	4	5	...	...	.	121	134	99	124	7	175	150	3d postfeeding day	3d day on 4 Gm.
L5	1	8	...	...	.	107	100							
	2	5	...	...	.	109	100							
	3	5	...	...	.	113	100							
	4	5	...	...	.	106	100	113	100	3	150	100	3d postfeeding day	No peak
N46	4 to 6	8	100	100	.	119	100	112	108	6	195	135	1st postfeeding day	2d postfeeding day
Cats with permanent polyuria														
166	1	8	377	371	7	349	346	587	614	7	740	770	2d postfeeding day	2d postfeeding day
D16	1	8	211	235	7	277	328							
	2	5	...	...	.	372	557							
	3	5	...	...	.	572	697	646	706	7	820	885	1st postfeeding day	1st postfeeding day
91	1	8	240	253	7	436	416	723	746	7	850	905	4th postfeeding day	2d postfeeding day
D5	1	8	308	343	7	441	445	427	448	7	600	675	1st postfeeding day	1st postfeeding day
125	4	6	164	168	7	220	241	217	224	7	265	315	Last day of feeding	Last day of feeding
168	4	5	124	143	7	268	256	326	340	7	510	500	2d postfeeding day	2d postfeeding day
Cats in which polyuria disappeared														
D6	1	8	121	100	7	110	112							
	2	3	...	...	.	133	128							
	3	8	...	...	.	142	159							
	4	2	...	...	.	120	127	202	208	6	240	250	4th postfeeding day	4th postfeeding day
D18	1	10	114	100	7	151	131	161	169	7	200	190	3d postfeeding day	3d postfeeding day
	1	16	118	105	7	167	146	181	199	11	225	225	10th postfeeding day	2d postfeeding day
Cats with subtotal removal of posterior lobe														
H1	1	8	108	100	7	142	117							
	2	5	...	...	.	260	253	212	241	4	375	395	1st postfeeding day	Last day on 2 Gm.
H2	1	8	108	100	7	106	104							
	2	5	...	...	.	87	100							
	3	5	...	...	.	80	100							
	4	5	...	...	.	113	137	101	139	7	180	180	Last day on 4 Gm.	2d postfeeding day

L 4 an average intake of water slightly higher than that attained by cat L 1 was observed during the period when 4 Gm. of thyroid was being fed daily. It should be noted that cats T 1, L 1, L 4 and L 5 showed little or no increase in water exchange after the administration of 1 or 2 Gm. of thyroid.

Effect of Salt.—As indicated in table 2 under the heading "Normal Cats," seven animals that had not been operated on were fed 2 or 3 Gm. of sodium chloride for one or two days. In all of these cats diuresis was elicited, the most marked being obtained in cat T 1. Table 2 shows that in this case 3 Gm. of salt was fed for two days, that the average output of urine for the two days preceding the feeding was 90 cc. and that the average intake of fluid was 100 cc. The first day that salt was given the output of urine increased to 165 cc. and the

TABLE 2.—*The Effect of the Feeding of Salt on the Water Exchange of Normal Cats and of Cats with Injury to the Supra-Optico-Hypophyseal System*

			Water Exchange Before Feeding			Water Exchange During Feeding				Water Exchange After Feeding		
						1st Day		2d Day				
Cat No.	Dose Gm.	Dose Time, Days	Aver. Amt. of Urine, Cc.	Aver. Amt. of Fluid, Cc.	Time, Days	Aver. Amt. of Urine, Cc.	Aver. Amt. of Fluid, Cc.	Aver. Amt. of Urine, Cc.	Aver. Amt. of Fluid, Cc.	Aver. Amt. of Urine, Cc.	Aver. Amt. of Fluid, Cc.	Time, Days
Normal Cats												
L1	3	2	70	100	1	145	100	110	160	100	100	3
L2	3	2	115	100	1	160	145	100	115	95	100	3
L4	3	1	95	100	1	195	155	160	165	80	100	3
T1	3	2	90	100	2	165	185	190	190	112	100	3
N7	3	1	67	95	2	155	180	...	...	107	100	2
N8	2	1	75	95	2	70	125	...	...	100	87	3
N10	3	1	132	95	2	140	150	...	...	115	100	3
Cats with Permanent Polyuria												
91	2	1	502	495	2	700	630	...	...	445	380	1
125	3	1	180	170	2	310	370	...	...	190	193	3
D32	3	2	330	360	2	525	625	515	535	386	385	4
Cats in Which Permanent Polyuria Disappeared												
D6	3	1	125	100	2	250	220	...	...	121	115	3
D6	3	2	112	100	2	205	230	185	225	141	108	3
D18	3	1	117	120	2	215	260	...	...	151	163	3
D18	3	2	140	137	2	180	255	260	215	150	113	3
Cats with Subtotal Removal of Posterior Lobe												
H1	3	2	105	117	2	230	255	260	260	121	128	3
H2	3	2	77	100	2	130	220	265	225	123	125	3

intake of fluid to 185 cc., while on the second day the output and intake each amounted to 190 cc. The 90 cc. of water consumed in this case probably gives the best measure of the intensity of the increase in the fluid exchange; in none of the other normal cats did the consumption of water equal this amount.

RESULTS IN CATS WITH PERMANENT POLYURIA

Effect of Thyroid.—In this group six cats were included, two with marked permanent polyuria (166 and D 16), two thyroidectomized cats with marked permanent polyuria (91 and D 5) and two with moderate permanent polyuria (125 and 168). These are listed in table 1 under the heading "Cats with Permanent Polyuria." The two cats with permanent polyuria and the two permanently polyuric thyroidectomized cats all showed marked increases in water exchange after the ingestion of 1 Gm. of thyroid daily for eight days, an amount which

had little or no effect on normal cats. The peak of the water exchange in cat 91 after the administration of thyroid was more than three times the average water exchange before the feeding, and in cat 166 there was a doubling of the fluid exchange as a result of the feeding of thyroid. The two cats with moderate polyuria also showed greater increases in the output of urine and the intake of fluid after receiving 4 Gm. of thyroid daily for five or six days than did the normal cats which received similar doses. In cat 168 the highest water exchange was about four times as great as the average exchange before the feeding of thyroid. It should be noted that in most instances the increases in the fluid exchange are much greater during the week after the cessation of the feeding of thyroid than they are during the actual period of feeding. Also, the peak of polyuria and polydipsia occurs in most cases during the first few days after the feeding is discontinued, after which there is a gradual diminution in the water exchange.

The Effect of Thyroidectomy.—Histologic examination of the removed glands showed that the thyroidectomy was complete in cats 91, D 5 and D 9. A parathyroid gland was found enclosed in a common capsule of connective tissue with each removed thyroid. The effect of thyroidectomy on the fluid exchange is indicated

TABLE 3.—*The Effect of Thyroidectomy and the Subsequent Feeding of Thyroid on the Water Exchange of Cats with Experimental Diabetes Insipidus*

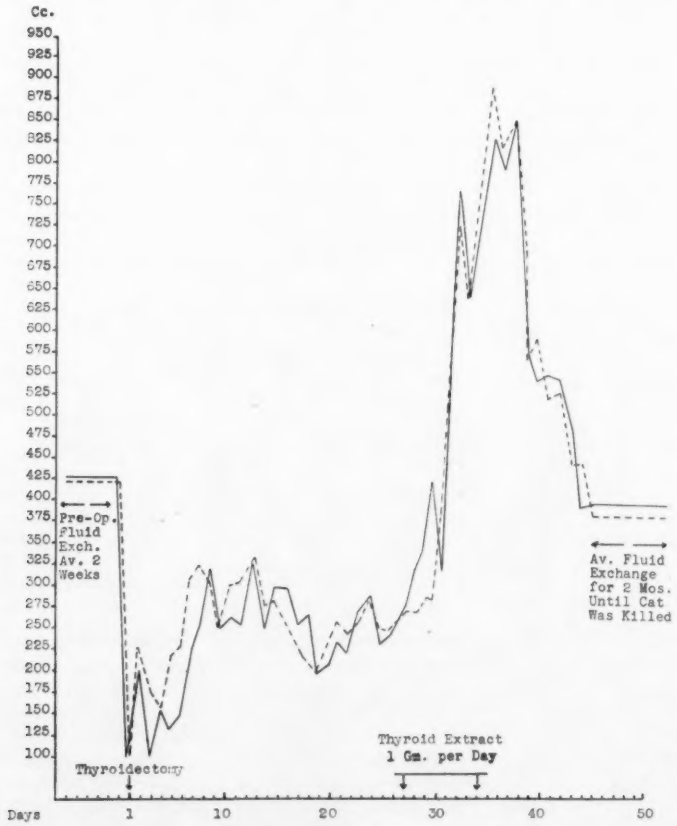
	Fluid Exchange 2 Weeks Before Feeding		Fluid Exchange Between Thyroidectomy and Thyroid Feeding			Peak Reached During Feeding		Fluid Exchange After Effect of Thyroid Had Passed		
Cat No.	Aver. Amt. of Urine, Cc.	Aver. Amt. of Fluid, Cc.	Aver. Amt. of Urine, Cc.	Aver. Amt. of Fluid, Cc.	Time, Days	Urine, Cc.	Fluid, Cc.	Aver. Amt. of Urine, Cc.	Aver. Amt. of Fluid, Cc.	Time, Days
91	341	425	233	252	25	850	905	404	386	60
D5	439	440	331	343	120	600	675	383	373	20
D9	471	499	308	338	12	Became sick and died at end of next 2 wks.				

in table 3. In cat 91 there was a reduction of nearly half the fluid exchange during the twenty-five days following thyroidectomy; e. g., the average daily output of urine was 431 cc. before and 233 cc. after operation. At the end of twenty-five days this animal was fed thyroid, as indicated in table 1, and an enormous diuresis resulted. The polyuria and polydipsia gradually decreased after the feeding was stopped, but instead of a return to the level of the fluid exchange prevailing before the feeding of thyroid, a level was maintained during the following two months which more nearly approximated the prethyroidectomy level, e. g., an average daily output of urine of 404 cc. and an average intake of fluid of 386 cc., as against 431 and 425 cc. before thyroidectomy. These results are graphically illustrated in the accompanying chart.

For four months following thyroidectomy cat D 5 showed a reduction in the fluid exchange of about one fourth, as compared with the preoperative level. The output of urine averaged 343 cc., as against 439 cc. during the two weeks before operation. During the feeding of thyroid marked diuresis developed (table 1). After the peak of this diuresis had passed the fluid exchange remained higher than before the feeding (as in cat 91) during the period from the seventh to the twenty-seventh day after the administration of thyroid was commenced. The animal was killed twenty-seven days after the feeding of thyroid

was begun. From the seventh to the twenty-seventh day the output of urine averaged 383 cc. and the intake of fluid 373 cc. In the last week the output was at as high a level as before thyroidectomy.

Cat D 9 showed a reduction in the fluid exchange of more than one-third after thyroidectomy, the average output of urine falling from 471 cc. before operation to 308 cc. during the twelve days after operation. At the end of that



Graph showing the effect of thyroidectomy and of the subsequent feeding of thyroid on the water exchange in a cat (cat 91) with diabetes insipidus. The solid line represents the output of urine; the broken line, the intake of fluid.

period the cat became ill and refused food. It died two weeks after the illness set in. During that period the fluid exchange decreased markedly. This animal was not fed thyroid.

The Effect of Salt.—The three animals (cats D 32, 91 and 125) with permanent diabetes insipidus showed greater absolute increases in the fluid exchange than did the normal controls. These cats are listed in table 2 under the heading "Cats

with Permanent Polyuria." The greatest increase in the output of urine among the normal cats as a result of the feeding of salt was 100 cc., and the greatest increase in the intake of fluid was 90 cc. These increases occurred on the second day of the feeding of salt in the case of cat T 1. On the other hand, cat 91 showed an increase in the output of urine of about 200 cc. when fed but 2 Gm. of salt for one day and an increase in the intake of water of 135 cc. The experimental feeding of salt was carried out on cat 91 many weeks before thyroidectomy was performed. Similar large increases were observed in the other two animals, cat 125, for example, showing an increase in the intake of water of 200 cc. on the day it received 3 Gm. of sodium chloride. Cat D 32 showed an increase in the intake of water of 265 cc. on the first day it received 3 Gm. of salt. After the cessation of the feeding of salt the water exchange quickly declined to normal limits, usually within twenty-four hours, in contrast to the prolonged after-effect of the feeding of thyroid.

RESULTS IN CATS IN WHICH MODERATE POLYURIA LATER DISAPPEARED

Effect of Thyroid.—The two animals (cats D 6 and D 18) in this group are listed in table 1. Cat D 6 showed the usual course of development of polyuria and polydipsia observed in cats with diabetes insipidus. There was an initial transient polyuria which disappeared, followed by the onset of the permanent phase of polyuria ten days after operation. During the three weeks immediately following the onset of the permanent phase the output of urine averaged 188 cc. daily and the intake of fluid 195 cc. Shortly thereafter this cat had a severe attack of distemper. For sixteen days little food was consumed, and the fluid exchange decreased markedly. However, the cat continued to drink small amounts of water (from 10 to 60 cc. daily) during this period of sickness. After the animal recovered from the distemper and commenced to eat again the polyuria did not return, although the occasional ingestion of small amounts of water gave warning that this was not a normal cat. Two months after recovery from the distemper this cat was fed progressively increasing doses of thyroid (table 1). Although it received less thyroid than three of the normal cats (T 1, L 4 and L 5), a considerably greater diuresis developed, at its peak the output being as high as 250 cc.

A similar disappearance of moderate polyuria took place in cat D 18, this time after recovery from a severe infection of the forelimbs and shoulders. In this case marked transient polyuria developed and gradually disappeared. It was followed by the onset of the permanent phase of the polyuria, on the tenth postoperative day. At the time of onset the severe infection was noted. During the next twelve days the cat consumed little food, but polyuria persisted, the output of urine averaging 205 cc. daily and the fluid intake 247 cc. At the end of this period the legs began to heal, and the animal consumed its full diet. At the same time the polyuria began to decrease, and within two weeks the fluid exchange was within normal limits. It remained normal for about two months, after which time the feeding of thyroid was commenced. During this two month period, however, small amounts of water were consumed on a number of occasions. Thyroid was administered at two different periods, separated by an interval of six weeks (cat D 18 is, therefore, listed twice in table 1). Considerable diuresis was elicited on both occasions with doses which had no appreciable effect on normal animals, the water exchange amounting to 225 cc. at its peak during the period immediately following the second feeding of thyroid.

The Effect of Salt.—Cats D 6 and D 18 were fed salt on two different occasions (table 2). Diuresis considerably greater than normal occurred in both these animals after the administration of 3 Gm. of sodium chloride. Thus, cat D 6 showed an increase in the output of urine of 125 cc. and an increase in the intake of fluid of 130 cc., while cat D 18 showed an increase in output of 120 cc. the second day it received 3 Gm. of salt. On another occasion cat D 18 increased its intake of fluid by 140 cc. the first day it received 3 Gm. of salt.

RESULTS IN CATS WHICH HAD UNDERGONE SUBTOTAL REMOVAL OF THE NEURO-INTERMEDIATE LOBE

The Effect of Thyroid.—The anatomic observations on the two cats which had undergone subtotal removal of the neuro-intermediate lobe have been reported in another place (Fisher, Ingram, Hare and Ranson[2]). At that time it was explained that in neither of these cats did polyuria develop spontaneously after the subtotal removal of the posterior lobe. It was believed, however, that the extirpation of most of the neuro-intermediate lobe should be followed by some disturbance in water metabolism, even though the damage to the antidiuretic mechanism was not severe enough to lead to permanent polyuria. It was thought that if these animals were subjected to the strain of diuresis some abnormality would be revealed. The results obtained with the feeding of thyroid in cat H 1 have confirmed this belief (table 1). It is evident that in cat H 1 marked diuresis, which amounted to 375 cc. at its peak, was elicited with amounts which had no appreciable effect on normal animals. On the other hand, although cat H 2 appeared to have had as great a deficiency of the neuro-intermediate lobe as had cat H 1, it failed to show diuresis which was significantly greater than that which could be obtained in a normal animal with equivalent doses.

The Effect of Salt.—As a result of the administration of salt cats H 1 and H 2 showed increases in water exchange which were greater than normal. The increase in cat H 2 was marked, a somewhat surprising result, in view of the fact that abnormal diuresis was not obtained with large doses of thyroid. On the second day that the animal received 3 Gm. of salt the output of urine increased by about 190 cc.

COMMENT

The results reported show clearly that cats with experimental diabetes insipidus due to injury of the supra-optico-hypophyseal system respond to such diuretics as salt and thyroid with a greater output of urine and a greater intake of fluid than do normal animals. It seems reasonable to suppose that this greater sensitivity toward diuretics is due to a deficiency in the organism of an antidiuretic substance, caused by injury to the supra-optico-hypophyseal system. Presumably this antidiuretic hormone is identical with or closely related to the pressor principle pitressin, which can be extracted from the posterior lobe of the pituitary body. It is therefore of interest that several investigators have reported changes in the content of pressor and antidiuretic substances in the body under varying conditions of water exchange. Thus,

Simon [5] and Simon and Kardos [6] found a decrease in the pressor and oxytocic content of the pituitary glands of rats, guinea-pigs and rabbits which had been subjected to a long period of thirst. This finding was interpreted as indicating an excess secretion of the posterior lobe, in an attempt to prevent the loss of fluid from the body under the condition of thirst, and a consequent diminution of the content in antidiuretic hormone of the secreting gland. Marx [7] reported an increase in the concentration of antidiuretic substance in the blood of fasting dogs and a decrease in the blood taken from a dog at the height of water diuresis. He was able to show that the blood from the fasting dog inhibited the polyuria of the heart-lung-kidney preparation in the same way as did solution of posterior pituitary, while the blood obtained from the dog at the height of diuresis had little or no inhibiting effect. Marx stated that the essential mechanism of water excretion consists of a diminution in the concentration of the antidiuretic substance and a consequent excretion of fluid by the kidney. He reported [8] that the pressor and antidiuretic substance in the blood has many properties in common with the substance obtained from the posterior lobe, and he stated the opinion that if it is not identical with the latter, at least it is closely related to it.

If Marx' view that at the height of diuresis there is a decrease in the concentration of the antidiuretic substance in the blood is accepted, the excessive diuresis obtained in our polyuric animals after the feeding of thyroid and salt can be explained in the following manner: A certain amount of antidiuretic hormone is present in the blood of normal subjects (Marx [8]). During diuresis the resistance which this hormone normally offers to the passage of fluid through the kidneys must be overcome. According to Marx this is accomplished by a decrease in the concentration of the hormone in the blood. In polyuric animals, however, there is already either a greatly reduced content or a complete disappearance of this substance from the blood. Consequently, there is little or no antidiuretic resistance to be overcome, and any tendency toward diuresis finds expression in an exaggerated form.

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5. Simon, A.: The Pressor and Oxytocic Content of the Hypophysis of Rats Under Various Conditions, Am. J. Physiol. **107**:220, 1934.

6. Simon, A., and Kardos, Z.: Ueber den Gehalt der Hypophysenhinterlappen normaler und durstender Tiere an blutdruck- und uteruswirksamen Stoffen, Arch. f. exper. Path. u. Pharmakol. **176**:238, 1934.

7. Marx, H.: Zur Theorie der Diurese, Klin. Wchnschr. **9**:2384, 1930.

8. Marx, H.: Die Bedeutung der Hypophyse für die Erkrankung der Niere, Klin. Wchnschr. **14**:367, 1935.

It may be pointed out also that several investigators (Malkin [9] and Dietel and Ditsch [10]) have found thyroid and posterior pituitary to be antagonistic in their effects on water metabolism. From this work it might be expected that a disturbance of the secretory activity of the posterior lobe following injury to the supra-optico-hypophyseal system would lead to an excessive diuretic response after the feeding of thyroid.

The excessive diuresis obtained in the two cats subjected to subtotal removal of the neuro-intermediate lobe (cats H1 and H2) and in the two animals in which moderate polyuria had disappeared (cats D6 and D18) may be explained in the same manner. In the latter two animals the postmortem observations showed that there was a partial destruction of the supra-optico-hypophyseal system, but in each case a considerable number of fibers from the supra-optico-hypophyseal tract escaped interruption. Both cat H 1 and cat H 2 had a remnant of the neuro-intermediate lobe which retained its innervation from the supra-optic nuclei. It seems reasonable to suppose, therefore, that in these four cats the partial destruction of the supra-optico-hypophyseal antidiuretic mechanism was associated with a subnormal content of antidiuretic hormone in the body, but a content still sufficiently great to prevent spontaneous polyuria. An abnormally high water exchange could be observed only under extreme conditions, such as prevail during diuresis due to salt or thyroid.

Several observations in regard to these four animals are somewhat difficult to explain. For example, although cat H2 showed excessive diuresis in response to the administration of sodium chloride, there was a normal response to that of thyroid. The remnant of the gland left in this case was certainly no larger than that found in cat H1. An explanation on the somewhat unsatisfactory basis of individual variation seems to be all that can be offered. A second difficulty is in connection with the disappearance after illness of the moderate polyuria observed in cats D6 and D18. Whether the illness was involved in the disappearance is difficult to decide. Since in both these animals the supra-optico-hypophyseal tracts were partially intact, the polyuria might have disappeared in the absence of illness. It may be noted, however, that the permanent cessation of polyuria, even moderate polyuria, has been a rare occurrence in our experience, although a temporary disappearance has been noted many times during periods of sickness. It has been pointed out (Fisher, Ingram, Hare and Ranson [2]) that the evidence

9. Malkin, S. J.: Ueber den Einfluss einiger Hormone auf den osmotischen Druck der Blutproteine, Klin. Wchnschr. **9**:551, 1930.

10. Dietel, F. G., and Ditsch, H.: Ueber den Einfluss von Hypophysenhinterlappenextrakt und Thyroxin auf den Wasser-, Natrium- und Chlorgehalt der Gewebe, Klin. Wchnschr. **13**:1174, 1934.

favors the view, first promulgated by von Hann,[11] that water metabolism is regulated by a sort of reciprocal action between the anterior and the posterior lobe of the hypophysis and that the diuretic processes in the body are under the control of the anterior lobe. It may well be that the illness in these two cats led to a disturbance of endocrine function which affected the latter processes. At any rate, there is a possibility that disturbances in water metabolism may result not only from the involvement of antidiuretic processes but from diuretic processes as well.

It has been suggested that diabetes insipidus is due to the diuretic activity of the anterior lobe of the pituitary body uncompensated by the antidiuretic action of the neuro-intermediate lobe (Fisher, Ingram, Hare and Ranson [2]). Several recent experiments have indicated possible ways in which the anterior lobe might exert its diuretic influence. Thus, Barnes, Regan and Bueno [12] and Biasotti [13] suggested that the diuresis elicited in dogs after the injection of acid and alkaline extracts of the anterior lobe was due to stimulation of the thyroid gland by the thyreotropic hormone of this lobe of the hypophysis. They found that the basal metabolic rate increased during the injections and that diuresis could not be elicited in animals previously thyroidectomized. Gaebler,[14] however, was able to obtain diuresis in thyroparathyroidectomized dogs after the injection of a commercial preparation of the anterior lobe of the hypophysis said to contain the growth hormone.[15] He stated that the diuretic effect cannot be readily correlated with the stimulation of the thyroid gland or with the increase in the metabolic rate, as has been suggested by Barnes, Regan and Bueno in the case of acid extracts. Later work by Dix, Rogoff and Barnes [16] also suggested that the diuresis is not necessarily associated with the stimulation of the thyroid gland. They found that the diuresis produced in normal animals by the administration of thyroid or extracts of the anterior lobe fails to occur in pancreatectomized dogs, although the metabolic rate is increased. The

11. von Hann, F.: Ueber die Bedeutung der Hypophysenveränderungen bei Diabetes insipidus, Frankfurt. Ztschr. f. Path. **21**:337, 1918.

12. Barnes, B. O.; Regan, J. F., and Bueno, J. G.: Is There a Specific Diuretic Hormone in the Anterior Pituitary? Am. J. Physiol. **105**:559, 1933.

13. Biasotti, A.: Thyroïde et action diurétique de l'extrait antéhypophysaire, Compt. rend. Soc. de biol. **115**:329, 1934.

14. Gaebler, O. H.: Effects of Thyroparathyroidectomy and Carbohydrate Intake on the Action of Anterior Pituitary Extracts, Am. J. Physiol. **110**:584, 1935.

15. The preparation used was antuitrin G.

16. Dix, A. S.; Rogoff, J. M., and Barnes, B. O.: Diuresis of Hyperthyroidism, Proc. Soc. Exper. Biol. & Med. **32**:616, 1935.

evidence, therefore, does not support the view that the diuretic action of the anterior lobe of the pituitary body is specific and mediated through the thyroid gland.

The results which we have reported on the effect of thyroidectomy in polyuric animals can be interpreted as further evidence against the theory that the diuretic action of the anterior lobe of the pituitary body is mediated through the thyroid gland. For if this were true, it might be expected that the removal of the thyroid gland from polyuric animals would bring about a cessation of polyuria. We have shown that such removal leads to a reduction of from a fourth to about a half of the fluid exchange. It is not certain, however, that the thyroidectomy is actually responsible for these decreases, since a number of our animals have shown spontaneous decreases of similar magnitude. The almost complete recovery to the prethyroidectomy level after the feeding of thyroid has been an interesting finding. This level was maintained in the case of cat 91 for two months, and at the end of twenty days cat D5 had attained the prethyroidectomy level, the output of urine on the day before the animal was killed amounting to 515 cc. We can conclude, therefore, that thyroidectomy in these animals causes a moderate decrease in the fluid exchange which can be restored by the feeding of thyroid and which apparently can be maintained at the higher level long after the effects of the thyroid have worn off.

It has been suggested (Fisher, Ingram, Hare and Ranson [2]), in agreement with Richter,[17] that the diuretic activity of the anterior lobe of the pituitary body is general and is brought about by the influence of this gland on growth, metabolism, activity and other phenomena. If the thyroid-stimulating effect is involved, it is only one of what is probably a complex series of processes making for diuresis. For, as Adolph [18] has pointed out: "It is apparent that the problem of water balance can never be settled alone. Only in the light of data concerning the regulation and interrelations of every other constituent and force of the cell and of the body can this familiar substance be fully appreciated."

SUMMARY

It has been shown that cats with experimental diabetes insipidus due to bilateral interruption of the supra-optico-hypophyseal tracts respond to such diuretics as thyroid and salt with a greater increase in water exchange than do normal cats. Also, cats with partial injury to the supra-optico-hypophyseal system in which permanent polyuria does not develop show similar abnormal increases in water exchange in response

17. Richter, C. P.: Experimental Diabetes Insipidus: Its Relation to the Anterior and Posterior Lobes of the Hypophysis, Am. J. Physiol. **110**:439, 1934.

18. Adolph, E. F.: The Metabolism and Distribution of Water in Body and Tissues, Physiol. Rev. **13**:336, 1933.

to these diuretics. The excessive diuresis in these cats has been interpreted as indicating an absence of or decrease in the amount of antidiuretic substance in the body.

The removal of the thyroid gland from three cats with permanent polyuria resulted in a diminution of the water exchange by from a fourth to a half. The subsequent feeding of thyroid to two of these animals brought on marked diuresis, which was followed by a return not to the prefeeding level but to a level more nearly corresponding to that prevailing before thyroidectomy. This new level persisted long after the effect of the thyroid had worn off. The evidence from these experiments does not support the theory that the diuretic effect of the anterior lobe of the pituitary gland is a specific effect mediated through the thyroid gland.

EFFECT OF ANOXEMIA ON THE EMPTYING TIME OF THE HUMAN STOMACH

INFLUENCE OF HIGH ALTITUDES

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In 1933,[1] attention was called to the fact that the condition of anoxemia is becoming important to an increasingly large number of people. All those who travel by airplane are subjected to a reduced tension of oxygen. There is a still larger group, who suffer from the effects of anoxemia which accompany various diseases. It is well known that anemia as well as certain pulmonary and circulatory disturbances may be complicated by anoxemia.

It was stated in previous papers [2] that hunger contractions as well as digestive peristalses are lessened by the production of anoxemia in the normal dog. In a subsequent paper [1] it was stated that anoxemia distinctly delays the emptying time of the stomach of the normal dog.

In the light of these observations, and especially since gastric symptoms are characteristic of the various disorders mentioned, it was considered well worth while to determine the effect of a lowered tension of oxygen on the emptying time of the normal human stomach.

METHOD

In order to produce an anoxemic condition, a special, steel respiratory chamber was constructed.[3] The chamber was cylindric and of sufficient size to accommodate comfortably two adults, either in a sitting or in a recumbent position. Windows were provided to serve as a means of communication between the occupants of the chamber and the operator, as well as to illuminate the interior. The chamber could be closed and sealed by an outside operator. The air was exhausted by a large rotary air pump, powered by a suitable electric motor. The capacity of the pump provided adequate ventilation. By means of three inlet valves, air was allowed to enter the chamber in any desired amount.

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1. Van Liere, E. J.; Crisler, G., and Robinson, D.: Effect of Anoxemia on the Emptying Time of the Stomach, Arch. Int. Med. **51**:796 (May) 1933.

2. Van Liere, E. J., and Crisler, G.: The Effect of Anoxemia on Hunger Contractions, Am. J. Physiol. **93**:267 (May) 1930. Crisler, G.; Van Liere, E. J., and Booher, W. T.: The Effect of Anoxemia on the Digestive Movements of the Stomach, ibid. **102**:629 (Dec.) 1932.

3. Van Liere, E. J.: A Respiratory Chamber for Producing Anoxemia in Man, J. Lab. & Clin. Med. **21**:963 (June) 1936.

The principle of producing anoxemia was simple: The air was drawn out faster than it was allowed to enter. The subject was placed in the chamber; the door was closed, and the air pump was started with all the inlet valves open. Then, by slowly closing the valves, the air in the chamber was decompressed to the desired degree and kept at that point. By the use of this method it was possible to secure a low tension oxygen, subject to easy control and yet to provide adequate ventilation for the subject within.

The chamber was connected with a mercury manometer, for the purpose of measuring the degree of decompression of the air. An altimeter was placed within the chamber, in view of the operator, as a further precautionary measure.

Eight normal young adult medical students volunteered for the work. They were given a standard meal,[4] which was prepared in the following manner: Fifteen grams of farina and 1 Gm. of salt were added to 350 cc. of boiling water and cooked until the total volume was 200 cc. The meal was allowed to cool, and to it was added 50 Gm. of barium sulfate, so that the emptying time of the stomach could be determined fluoroscopically. The meal was eaten without difficulty.

The standard meal was always given at 8:30 a. m., the subject having received no other food since the preceding evening. Each man ate the meal several times, and a figure for the normal emptying time of the stomach at atmospheric pressure was established. During the time in which the determination was being made, the subject was requested to relax both physically and mentally as much as possible. After a constant normal figure had been established for each subject, he was given the meal as usual but was placed in the respiratory chamber immediately after he finished eating. The air in the chamber was then decompressed to the desired degree and kept at that point.

An experimental margin of plus or minus fifteen minutes was allowed to compensate for the time needed to remove the subject from the chamber and to examine him under the fluoroscope.

Determinations of the emptying time of the stomach were made at manometric pressures of 560 mm., 515 mm. and 460 mm., corresponding with altitudes of approximately 8,000, 10,000 and 14,000 feet, respectively. The respective percentages of oxygen at these altitudes are: 15.37, 14.25 and 12.28. Several determinations were made at each pressure. Two students were subjected to an altitude of 18,000 feet, which corresponds to a percentage of oxygen of 10.56.

RESULTS

The accompanying table and chart show and summarize the results obtained.

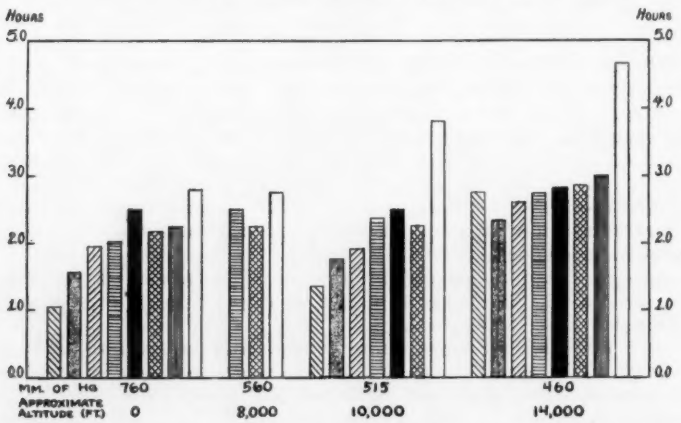
Effect of Anoxemia on the Emptying Time of the Stomach

Subject No.	Normal, 0 Feet Hours	560 Mm. of Mercury, 8,000 Feet		515 Mm. of Mercury, 10,000 Feet		460 Mm. of Mercury, 14,000 Feet	
		Hours	Percentage of Delay	Hours	Percentage of Delay	Hours	Percentage of Delay
1	1.03	....	....	1.33	29.1	2.75	166.9
2	1.55	....	....	1.75	12.9	2.33	50.3
3	1.94	....	....	1.90	−2.0	2.60	34.0
4	2.02	2.50	23.7	2.37	17.3	2.75	35.6
5	2.50	....	....	2.50	0.0	2.83	13.2
6	2.17	2.25	3.6	2.25	3.6	2.87	32.5
7	2.25	....	....	....	....	3.00	33.3
8	2.80	2.75	−1.8	3.81	36.1	4.67	66.7
Average	2.03	....	8.5	....	13.9	2.98	54.1

4. Personal communication of F. A. Hellebrandt.

It will be seen that there was considerable variation in the normal emptying time of the stomach, the extreme limits being one hour and two and eight-tenths hours, respectively. The average normal time for the eight persons was approximately two hours.

There was definite prolongation of the emptying time of the stomach of two of the three subjects on whom determinations were made at 560 mm. of mercury. The emptying time of the stomach of the third man was shortened slightly. Six of the seven subjects on whom determinations were made at 515 mm. of mercury showed prolongation, while one was refractory at this pressure. Determinations were made on all eight subjects at 460 mm. of mercury, and all showed appreciable prolongation. At this pressure the emptying time of the stomach was



Effect of anoxemia on the individual emptying time of the stomach in eight subjects at various pressures. Each subject is represented by the same type of shading throughout.

in no case prolonged less than 13.2 per cent of normal, and in one case it was 166.9 per cent of normal.

COMMENT

The figures that we obtained for the normal emptying time of the stomach may seem low. It must be remembered, however, that the meal was not large and that it consisted practically entirely of carbohydrate. Since the size and nature of the meal were constant throughout the experiment, we feel that the figures constitute an accurate basis for determining the effects of the experimental conditions. In order to check the accuracy of the normal figures, certain subjects were given the standard meal and placed in the chamber with the door closed and

the motor running but with all the inlet valves open so that the air in the chamber remained at atmospheric pressure. In each case except one, the figure obtained for the normal emptying time of the stomach was identical with that previously established as normal. In the one case the emptying time was slightly shorter than it was outside the chamber. This variation occurred in an active and alert person; the interpretation is that the removal of extraneous influences was responsible for the change.

Great care was exercised in decompressing the air in the chamber as well as in allowing the pressure to return to normal. As a rule it took about five minutes to decompress the air to make it correspond to an altitude of 14,000 feet, and it took the same length of time to allow the air to come back to atmospheric pressure. Unless care was taken in this regard, the men complained of pain in the middle ear. The only other subjective complaint was of an occasional slight headache which would disappear an hour or two after the subject had been removed from the chamber. None of the subjects, however, expressed real apprehension and all willingly returned to the chamber. The psychic factor, therefore, must have been very slight. This is further borne out by the fact that the results of experiments on man described in this paper closely parallel those of the experiments performed on dogs which were reported previously.[1] One must be careful, however, not to draw too close a parallel between the two sets of experiments, as the dogs received considerable protein and fat in their meal, while the meal used for the men consisted practically entirely of carbohydrate. The difference between the food given to the dogs and that given to the men becomes increasingly significant in view of what Hellebrandt and her associates [5] have shown concerning the parallel in function between the mechanism which controls the secretion of the stomach and that which determines its motility.

It is interesting to note that there is considerable individual variation in the response to anoxemia. At a pressure of 560 mm. of mercury, corresponding to 15.35 per cent of oxygen and 8,000 feet altitude, two of three men showed a prolongation in gastric evacuation; the other showed a slight acceleration. The acceleration of emptying time was noted also in another person at 515 mm. of mercury, or about 10,000 feet altitude. At this pressure the other six men showed a definite prolongation. In one case as much as 36.1 per cent more than normal time was required; this condition was observed in the same person in whom the rate of gastric emptying was accelerated at 560 mm. of

5. Hellebrandt, F. A.; Baerstein, H. D., and Hoopes, S. L.: Studies in the Influence of Exercise on the Digestive Work of the Stomach, Am. J. Physiol. **107**:370 (Feb.) 1934.

mercury. We have concluded from our work that the threshold for the average person lies between 6,000 and 8,000 feet.

At 460 mm. of mercury, which corresponds to an altitude of 14,000 feet and to an oxygen pressure of 12.28 per cent, each subject showed definite prolongation of gastric evacuation. Two subjects were highly susceptible, the normal emptying time being prolonged by 66.7 per cent and 166.9 per cent, respectively. For the other six men the average prolongation was about 35 per cent.

Two men were subjected to a pressure of 380 mm. of mercury, which corresponds to an altitude of about 18,000 feet. Although the result lay in the same direction, it was less striking than might be anticipated. One of the men complained of severe dizziness and intense headache; the latter symptom persisted for from eight to ten hours after he had been removed from the chamber. For the most part, however, the pressures used in this work correspond with altitudes common in the Rocky Mountain region of the United States and the high plateaus of the Southwest. It is hardly necessary to point out that the native of those regions is undoubtedly well acclimated and in all probability the emptying time of the stomach would be normal.

It is to be noted that the results under consideration were obtained on a subject at complete rest. There is good reason to believe that even mild exercise at a high altitude would influence the rate of gastric evacuation considerably. We are hoping to conduct experiments that will verify this hypothesis.

In a recently published article Crisler, Van Liere and Wiles,[6] after working on dogs, pointed out that the delay in gastric emptying time during anoxemia is on a vagospastic pylorospastic basis until a critical threshold is reached; after this point has been passed, further delay is undoubtedly caused by a loss in gastric motility. There is every reason to believe that the same factors are operative in man. Another mechanism, however, must be mentioned. It is generally accepted today that epinephrine is given off during anoxemia. Epinephrine could well cause a definite inhibition of motility of the stomach, as has been shown in a recent paper.[7]

SUMMARY AND CONCLUSIONS

A comparatively simple method of producing anoxemia in man is briefly described.

6. Crisler, G.; Van Liere, E. J., and Wiles, I. A.: The Mechanism of the Delay in Gastric Emptying Time Caused by Anoxemia, Am. J. Digest. Dis. & Nutrition **2**:221 (June) 1935.

7. Van Liere, E. J.; Lough, D. H., and Sleeth, C. K.: The Effect of Ephedrine on the Emptying Time of the Human Stomach, J. A. M. A. **106**:535 (Feb. 15) 1936.

It was found that under carefully controlled conditions normal adults showed a definite prolongation of the emptying time of the stomach when subjected to anoxemia. The degree of retardation of gastric emptying time varies in the same direction as the degree of anoxemia but in no definite ratio.

The threshold for the average person at rest probably lies between 6,000 and 8,000 feet.

At a pressure of 560 mm. of mercury, corresponding with 15.35 per cent oxygen and 8,000 feet altitude, two of three men showed a definite prolongation of gastric emptying time. The third man proved susceptible at a higher degree of anoxemia. One man was refractory at 515 mm. of mercury (10,000 feet) but responded at 460 mm. of mercury. At the latter pressure, corresponding to an altitude of 14,000 feet and an oxygen pressure of 12.50 per cent, each subject showed a definite prolongation of the emptying time of the stomach—in no case less than 13.2 per cent of the normal time and in one case 166.9 per cent of the normal. Two men were subjected to an altitude of 18,000 feet; the result lay in the same direction.

A brief discussion as to the mechanism involved in the retardation of gastric evacuation appears in the body of the paper.

We feel that since many diseases of man are accompanied by anoxemia and since residence at high altitudes during summer is becoming more and more popular and also since airplane travel is rapidly increasing, these experiments are of distinct interest to clinical medicine.

Besides the two junior authors of this paper the following men served as subjects: K. Gerchow, J. Holt, D. Jones, R. Martin, C. Polan and J. Stratton.

RED BLOOD CELL VALUES FOR NORMAL MEN AND WOMEN

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The fundamental importance of accurate standards for hemoglobin content, number of red blood cells and volume of packed cells in the venous blood of normal persons is definitely recognized. Application of these normal values to the study of the various forms of anemia has given the standards clinical as well as academic importance. Possible variations in the normal range of values can be investigated only by comparison of the results of analyses of samples of blood from persons living in a number of widely separated localities which differ in climate and altitude. This comparative study may ultimately make possible the adoption of universal standards or may necessitate the establishment of separate standards for different regions.

Extensive studies of the venous blood of adults have been made in the United States by Haden,[1] in Kansas City, Mo., Cleveland and Detroit; Osgood and Haskins,[2] in Portland, Ore.; Wintrobe and Miller,[3] in New Orleans, and Wintrobe,[4] in Baltimore; Foster and Johnson,[5]

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The experimental data in this paper were taken from the thesis submitted by Marjory I. Andresen to the Graduate School of the University of Colorado, in June 1934, in partial fulfilment of the requirements for the degree of Master of Science.

1. Haden, R. L.: (*a*) Clinical Significance of Volume and Hemoglobin Content of the Red Blood Cell, Arch. Int. Med. **49**:1032 (June) 1932; (*b*) Personal communication to the authors.

2. Osgood, E. E.: (*a*) Hemoglobin, Color Index, Saturation Index and Volume Index Standards, Arch. Int. Med. **37**:685 (May) 1926. (*b*) Osgood, E. E., and Haskins, H. D.: Relation Between Cell Count, Cell Volume and Hemoglobin Content of Venous Blood of Normal Young Women, ibid. **39**:643 (May) 1927.

3. Wintrobe, M. M., and Miller, M. W.: Normal Blood Determinations in the South, Arch. Int. Med. **43**:96 (Jan.) 1929. Wintrobe, M. M.: Hemoglobin Standards in Normal Men, Proc. Soc. Exper. Biol. & Med. **26**:848, 1929; Blood of Normal Young Women Residing in a Subtropical Climate, Arch. Int. Med. **45**:287 (Feb.) 1930.

4. Wintrobe, M. M.: Blood of Normal Men and Women, Bull. Johns Hopkins Hosp. **53**:118 (Sept.) 1933.

5. Foster, P. C., and Johnson, J. R.: Oxygen Capacity and Hemoglobin Content of Normal Blood of Men, Proc. Soc. Exper. Biol. & Med. **28**:929, 1931.

in New Orleans, and Walters,[6] in Lawrence, Kan. None of these cities has an altitude of more than 1,000 feet (304 meters) above sea level.

Wintrobe [7] proposed values for the individual red blood cell, which he termed the corpuscular constants. These values include the volume of the average cell in cubic microns (mean corpuscular volume), the hemoglobin content in micromicrograms (mean corpuscular hemoglobin) and the concentration of the hemoglobin in percentage of unit volume (mean corpuscular hemoglobin concentration). These values are not based on arbitrary standards and are therefore useful in the comparison of the data from different parts of the country. A comparison of such data reveals certain similarities, particularly of the mean corpuscular hemoglobin concentration. It also reveals differences, as of the mean corpuscular volume, which are probably not wholly attributable to technic. Until further studies are reported, the assumption cannot be made that the values for individual corpuscules are everywhere the same.

It is usually stated that with an increase in altitude there is a progressive rise in the number of red blood cells and in the hemoglobin content. The magnitude of this change and the effect on the corpuscular constants have not been thoroughly investigated. Smith, Belt, Arnold and Carrier [8] observed that after the subject had spent four weeks at an elevation of 11,000 feet (3,352 meters) the red blood cells were smaller than those observed when the patient lived at sea level but the concentration of hemoglobin was increased. A period of four weeks may not be sufficient to allow stabilization of these values after a change of altitude. The values obtained by Smith and his co-workers may not be strictly comparable therefore to Hurtado's [9] observations on one hundred and thirty-two Indians of the Peruvian Andes, who had been lifelong residents at an altitude of more than 10,000 feet (3,048 meters). Hurtado found that the individual corpuscles were larger but showed a lower hemoglobin concentration than those of persons living at sea level. He expressed the belief that the adaptation to altitude is not primarily in the increase of red blood cells and hemoglobin but rather in the development of a larger surface area in the individual corpuscles, with a decrease in the hemoglobin concentration. Other factors, such as diet, race and environmental conditions, besides altitude

6. Walters, O. S.: Normal Erythrocyte, Hemoglobin and Packed Cell Volume Standards in Young Men, J. Lab. & Clin. Med. **19**:851 (May) 1934.

7. Wintrobe, M. M.: The Volume and Hemoglobin Content of the Red Blood Corpuscle, Am. J. M. Sc. **177**:513 (April) 1929.

8. Smith, H. P.; Belt, A. E.; Arnold, H. R., and Carrier, E. B.: Blood Volume Changes at High Altitudes, Am. J. Physiol. **71**:395 (Jan.) 1925.

9. Hurtado, Alberto: Studies at High Altitude, Am. J. Physiol. **100**:487 (May) 1932.

must be considered when Hurtado's observations are compared with those reported in this country.

The present study supplies some data on the volume, hemoglobin content and number of red blood cells in the venous blood of average normal adults living at an altitude of about 5,000 feet (1,524 meters). It is also designed to furnish a basis for comparison with a similarly conducted investigation of the blood of children, which is still in progress.

SUBJECTS

The subjects of the investigation were forty white men and forty white women of various nationalities. The group included physicians, medical students, technicians and office workers between 20 and 45 years of age. They were in apparent good health and had been constant residents of this region for at least two years. The work was begun in December and was carried on through the winter, spring and summer months. On fourteen men and eighteen women of the series determinations were repeated at intervals of from seven to fourteen days for a total of six examinations each, and the averages were used in the data for the series.

METHODS

Venous blood and capillary blood are considered equivalent [10] when care is used in obtaining samples from both sources. Since the more accurate methods of analysis require the use of blood in amounts obtainable only by venipuncture, only samples of venous blood were used in the present study.

Blood was withdrawn from a vein in the arm, usually between the hours of 9 and 12 in the morning, while the subject was engaged in the usual activities of the day. In securing blood from women no attention was paid to the menstrual cycle, as recent work of Reich and Green [11] has indicated that menstruation produces no significant changes in the values for red blood cells and hemoglobin. Care was taken to avoid undue stasis in the arm from which the sample was collected. The blood was thoroughly mixed in a test tube with 2 mg. of dry, iron-free, neutral potassium oxalate for each cubic centimeter of blood. This oxalated specimen was used for all procedures.

Red blood cell counts were made on at least two dilutions from each sample of blood. These were repeated until results differing by less than 200,000 cells were obtained, and the average was taken. Hayem's diluting fluid and a Levy-Hausser counting chamber and Thoma pipets certified by the Bureau of Standards were used for all counts.

The cell volume was determined for the first fourteen men of the series by the use of Van Allen [12] hematocrit tubes. These were then replaced by the Wintrobe [13] hematocrit tubes, which were found to be more accurate. Samples were centrifugated at 3,000 revolutions per minute in an international centrifuge, type S. B.,

10. Osgood, E. E., and Haskins, H. D.: Laboratory Diagnosis, Philadelphia, P. Blakiston's Son & Co., 1931, p. 345.

11. Reich, C., and Green, D.: Red Cell Regeneration during the Menstrual Cycle, Arch. Int. Med. **49**:534 (March) 1932.

12. Van Allen, C. M.: An Hematocrit Method, J. Lab. & Clin. Med. **10**:1027 (Sept.) 1925.

13. Wintrobe, M. M.: A Simple and Accurate Hematocrit, J. Lab. & Clin. Med. **15**:287 (Dec.) 1929.

for thirty minutes; a reading of the height of the column of red cells was taken, and centrifugation was continued for five minute periods until there was no further change in volume. The amount of shrinkage due to the potassium oxalate was found by dividing the samples of blood from thirty subjects between tubes containing potassium oxalate and tubes containing heparin. Hematocrit determinations were made simultaneously on the two portions. The average shrinkage from the potassium oxalate was found to be 6.4 per cent, and this correction was made on all the oxalated specimens. On ten of the thirty samples hirudin was also used as an anticoagulant. Six of the ten samples treated with hirudin gave readings identical with those of the heparinized blood, and the maximum difference in any of the other four samples was 0.4 per cent.

Three methods for the determination of hemoglobin were followed as a routine. The Van Slyke-Neill[14] manometric method of gas analysis was used as the standard research procedure to determine the oxygen-carrying capacity of the hemoglobin. From the oxygen capacity in cubic centimeters the hemoglobin content was calculated on the assumption that 1 Gm. of hemoglobin combines with 1.34 cc. of oxygen. This factor, though it is in general use for the standardization of clinical instruments by the oxygen capacity method, is based on Hüfner's[15] analysis of ox blood, and its applicability to human blood has been questioned.[16] It was used in the present study to afford comparison with other data, which are reported in grams.

The determination of hemoglobin from the iron content of the whole blood is often mentioned as a method approaching the Van Slyke technic in research accuracy. The procedure followed consisted of a modification of the original method of Wong.[17] One cubic centimeter of whole blood was diluted with 4 cc. of distilled water, and 1 cc. of the diluted blood was digested with concentrated sulfuric acid and potassium chlorate. After digestion was complete, the material was diluted to about 10 cc. with distilled water, and a drop of saturated potassium persulfate was added to prevent reduction of the iron. The color was developed by the addition of 5 cc. of a three times normal solution of potassium sulfocyanate and was immediately extracted by shaking with exactly 25 cc. of a mixture of 2 parts of ethyl ether and 5 parts of amyl alcohol. The use of this extraction mixture was taken from the method of Stokes and Cain as described by Reich and Tiedemann.[18] Comparison was made colorimetrically with a standard iron solution digested and treated in exactly the same manner as the unknown. The oxygen capacity of the blood was figured from the iron content on the basis[19] that one milligram atom, or 55.9 mg., of iron binds one milligram molecule, or 22.4 cc., of oxygen measured at 0 C. and at a pressure of 760 mm. of mercury.

14. Van Slyke, D. D., and Neill, J. M.: The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, J. Biol. Chem. **61**:523 (Sept.) 1924.

15. Hüfner, G.: Neue Versuche zur Bestimmung der Sauerstoffcapacität des Blutfarbstoffs, Arch. f. Physiol., 1894, p. 130.

16. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol. 1, p. 524.

17. Wong, S. Y.: Colorimetric Determination of Iron and Hemoglobin in Blood, J. Biol. Chem. **55**:421 (March) 1923.

18. Reich, C., and Tiedemann, V. G.: A Study of Iron Volume Index of the Blood and Its Significance in the Treatment of Anemia, Am. J. M. Sc. **184**:637 (Nov.) 1932.

19. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 672.

The Osgood-Haskins [20] method of hemoglobin estimation after conversion to acid hematin was selected as one of the more accurate clinical procedures. The hemoglobin content in grams was calculated from the special table provided with the standard.[21]

Certified glassware was used in the determination of hemoglobin by the iron and the acid hematin method. The chamber of the Van Slyke apparatus and the hematocrit tubes were carefully recalibrated. Colorimetric work was done in a

TABLE 1.—*Values for Venous Blood of Normal Men*

	Hemoglobin, Grams in 100 Cc. of Blood			Volume of Packed Cells, Cc. per 100 Cc. of Blood	Red Blood Cells, Millions per Cu. Mm.	Mean Corpuscular Hemoglobin	Mean Corpuscular Volume	Mean Corpuscular Hemoglobin Concentration
	Oxygen Capacity Method	Iron Method	Acid Hematin Method					
1*	18.3	18.3	18.6	53.6	5.38	34.0	99.6	34.1
2*	18.0	18.0	18.3	50.6	5.76	31.2	87.8	35.5
3	17.9	17.9	17.5	51.4	5.99	29.8	85.8	34.8
4	17.7	17.6	17.5	48.1	5.49	32.2	87.6	36.8
5	17.5	17.2	17.3	50.6	5.78	30.2	87.5	34.5
6	17.4	17.6	17.9	51.2†	5.33	32.6	96.0	33.9
7	17.3	17.3	17.3	48.0	5.45	31.7	88.0	36.0
8*	17.2	17.1	17.2	49.7	5.70	30.1	87.1	34.6
9	17.2	17.2	17.3	51.7	5.32	32.3	97.1	33.2
10	17.1	16.5	16.1	49.8	5.53	30.9	90.0	34.3
11*	17.1	17.0	16.8	47.7	5.28	32.3	90.3	35.8
12*	17.0	16.8	17.5	48.5	5.41	31.4	89.6	35.0
13*	16.9	16.5	17.6	47.6	5.69	29.7	83.6	35.5
14	16.8	16.8	16.4	48.6	5.65	29.7	86.0	34.5
15*	16.8	16.5	16.9	47.4	5.02	33.4	94.2	35.4
16*	16.8	16.5	17.2	49.0	6.07	27.6	80.7	34.2
17	16.8	16.3	16.6	49.0†	5.49	30.6	89 2	34.2
18*	16.8	16.4	16.9	51.7	5.67	29.6	91.1	32.4
19	16.7	....	16.7	48.4	5.22	31.9	92.7	34.5
20	16.7	16.6	....	48.0	5.44	30.7	88.2	34.7
21*	16.6	16.5	17.4	46.6	5.34	31.0	87.2	35.6
22	16.4	16.6	18.1	49.2†	5.28	31.0	93.1	33.3
23	16.4	15.9	16.0	49.0†	5.57	29.4	87.9	33.4
24	16.3	16.0	17.2	50.1	5.34	30.5	93.8	32.5
25	16.3	16.6	....	49.0	5.38	30.3	91.0	33.2
26	16.2	16.2	17.2	47.2	5.50	29.4	85.8	34.3
27	16.2	15.9	18.0	48.2†	5.26	30.8	91.6	33.6
28*	16.2	15.8	16.8	47.7	5.52	29.3	86.4	33.9
29*	16.1	16.3	16.5	48.9	5.33	30.2	91.7	32.9
30*	16.0	15.8	17.0	47.0	5.40	29.6	87.0	34.0
31	15.9	15.7	16.4	49.0	5.47	29.0	89.5	32.4
32	15.9	15.2	16.6	45.7	5.43	29.2	84.1	34.7
33*	15.8	15.2	16.1	44.9	5.19	30.4	86.5	35.1
34	15.6	15.5	16.4	47.5	5.33	29.2	89.1	32.8
35	15.5	15.8	14.5	46.2	5.08	30.5	90.9	33.5
36	15.5	15.1	16.8	48.6	5.68	27.2	85.5	31.8
37	15.4	15.9	14.9	44.0	4.99	30.8	88.1	35.0
38	15.3	15.8	15.4	46.6	5.23	29.2	89.1	32.8
39	15.2	15.2	15.3	43.8	5.02	30.2	87.2	34.7
40	15.0	....	....	44.3	4.83	31.0	91.7	33.8
Mean	16.54	16.51	16.87	48.35	5.42	30.5	89 2	34.2

* Average of six determinations.
† Heparin used as an anticoagulant.

dark room, the same Bausch and Lomb Duboscq colorimeter being used for all readings, with a Bausch and Lomb colorimeter illuminator as the constant source of light.

COMMENT

Results obtained from 240 determinations on the forty men and forty women who comprise the present series are listed in tables 1 and 2.

20. Osgood, E. E., and Haskins, H. D.: A New Permanent Standard for Estimation of Hemoglobin by Acid Hematin Method, J. Biol. Chem. **57**:107 (Aug.) 1923.

21. The standard and table were furnished by Dr. E. E. Osgood.

From thirty-six men and thirty-nine women sufficient blood was obtained for determinations of hemoglobin by all three methods. The mean values in grams for these members of the series are given in table 3.

The general averages for the values obtained by the three methods are in close agreement. The values obtained by the Osgood-Haskins

TABLE 2.—*Values for Venous Blood of Normal Women*

	Hemoglobin, Grams in 100 Cc. of Blood			Volume of Packed Cells, Cc. per 100 Cc. of Blood	Red Blood Cells, Millions per Cu. Mm.	Mean Corpuscular Hemoglobin	Mean Corpuscular Volume	Mean Corpuscular Hemoglobin Concentration
	Oxygen Capacity Method	Iron Method	Acid Hematin Method					
1*	15.8	15.7	15.8	45.9	4.75	33.2	96.6	34.4
2	15.6	15.0	15.7	44.0	4.71	33.1	93.4	35.4
3*	15.4	15.5	14.9	45.0	5.00	30.8	90.0	34.2
4*	15.2	15.3	15.3	44.9	4.66	32.6	96.3	33.8
5*	15.2	15.2	14.7	42.7	4.48	33.9	95.3	35.5
6*	15.3	15.5	15.0	44.2	4.58	33.4	96.5	34.6
7*	14.9	15.0	14.3	44.2	4.51	33.0	98.0	33.7
8	15.0	15.5	14.8	44.9	4.61	32.5	97.3	33.4
9	14.9	15.6	15.4	45.5	4.73	31.5	96.1	32.7
10	14.9	14.1	14.0	44.5	4.78	31.1	93.0	33.4
11	14.8	14.6	14.9	46.1	4.84	30.5	95.2	32.1
12	14.7	15.0	14.6	45.3	4.79	30.6	94.5	32.4
13*	14.9	15.0	14.4	43.6	4.57	32.6	95.4	34.1
14*	14.8	14.9	14.1	44.1	4.61	32.1	95.6	33.5
15*	14.8	14.6	14.6	43.4	4.48	33.0	96.8	34.1
16	14.7	14.7	15.3	44.0†	4.58	32.0	96.0	33.4
17	14.7	15.1	15.3	43.7†	4.94	29.7	88.4	33.6
18*	14.7	14.6	14.1	42.6	4.55	32.3	93.6	34.5
19	14.5	14.4	....	43.6	4.63	31.3	94.1	33.2
20	14.5	14.0	14.4	42.7†	4.71	30.7	90.6	33.9
21	14.4	14.0	14.7	44.0†	4.78	30.1	92.0	32.7
22*	14.5	14.5	14.2	43.3	4.59	31.5	94.3	33.4
23	14.4	15.3	13.9	42.4	4.82	29.8	87.9	33.9
24	14.4	15.0	14.2	42.6	4.50	32.0	94.6	33.8
25*	14.4	14.5	13.9	42.6	4.53	31.8	94.0	33.8
26*	14.3	14.5	14.1	41.5	4.47	31.9	92.8	34.4
27*	14.4	14.3	14.1	41.7	4.48	32.1	93.0	34.5
28	14.3	15.0	15.4	46.0	4.62	30.9	99.5	31.0
29	14.3	14.1	13.9	44.2†	4.66	30.6	94.8	32.3
30	14.1	14.1	13.6	43.4	4.54	31.0	95.5	32.4
31	14.1	14.0	13.6	42.9	4.62	30.5	92.8	32.8
32*	14.1	14.0	13.5	41.5	4.55	30.9	91.2	33.9
33	14.0	14.3	13.6	41.3	4.41	31.7	93.6	33.9
34*	14.0	14.3	14.1	42.4	4.65	30.1	91.1	33.0
35	13.9	13.7	14.0	43.9†	4.76	29.2	92.2	31.6
36*	13.6	13.6	13.7	39.9	4.46	30.4	89.4	34.0
37*	13.5	13.5	13.4	41.1	4.45	30.3	92.3	32.8
38	12.9	12.7	13.2	41.1	4.52	28.5	90.9	31.3
39	12.7	12.4	12.7	37.1	4.67	27.1	79.4	34.2
40	12.7	13.1	13.5	41.0†	4.63	27.4	88.5	30.9
Mean	14.45	14.51	14.33	43.22	4.63	31.2	93.3	33.4

* Average of six determinations.
† Heparin used as an anticoagulant.

acid hematin method checked almost as closely with those from the Van Slyke determinations of oxygen capacity as did those obtained by the iron method.

The frequency distribution of the hemoglobin content in grams as determined by the Van Slyke-Neill oxygen capacity method, of the number of red blood cells and of the volume of packed cells is given in chart 1. Values for corpuscular constants calculated from these figures are graphically shown in chart 2.

Comparison of the mean values with those previously reported by other workers is shown in table 4. All volumes of packed cells are corrected to the volume of heparinized blood.

TABLE 3.—*Mean Values for Hemoglobin in Grams per Hundred Cubic Centimeters of Blood*

Men	Method	Mean*	Standard Deviation*	Coefficient of Variation,* Percentage
36	Oxygen capacity	16.58 ± 0.092	0.82 ± 0.065	4.9
36	Iron content	16.51 ± 0.095	0.84 ± 0.067	5.1
36	Acid hematin	16.87 ± 0.101	0.93 ± 0.072	5.5
Women				
39	Oxygen capacity	14.45 ± 0.074	0.69 ± 0.052	4.7
39	Iron content	14.51 ± 0.086	0.80 ± 0.061	5.5
39	Acid hematin	14.33 ± 0.073	0.68 ± 0.052	4.7

* Computation of statistical data in frequency groups is used in this study (Dunn, H. L.: Application of Statistical Methods in Physiology, Physiol. Rev. **9**: 341 [April] 1929).

TABLE 4.—*Values for Venous Blood Reported in the United States*

Authority and Location	Number in Series	Hemoglobin, Gm. per 100 Cc. of Blood	Volume of Packed Cells in Cc. per 100 Cc. of Blood	Red Blood Cells in Millions per Cu. Mm.	Mean Corpuscular Hemoglobin, Micromicrograms	Mean Corpuscular Volume, Cubic Microns	Mean Corpuscular Hemoglobin Concentration, Percentage
Osgood, Haskins and Trotman (J. Lab. & Clin. Med. **17**: 859 [June] 1932), Portland, Ore.	196 men	15.80	46.35	5.4	29.2	85.8	34.0
	100 women	13.70	42.43	4.8	28.5	88.3	32.2
Wintrobe and Miller,[3] New Orleans	100 men	17.0	49.6	5.85	29.0	84.7	34.2
	50 women	13.76	41.5	4.93	28.0	84.1	33.1
Haden,[1] Kansas City, Mo., Detroit and Cleveland	70 men	15.34	45.5	4.95	31.0	92.0	33.7
	30 women	13.37	39.8	4.38	30.5	91.0	33.5
Foster and Johnson,[5] New Orleans	40 men	15.74	46.7	5.26	29.9	88.7	33.6
Walters,[6] Lawrence, Kan.	100 men	15.12	46.5	4.84	31.4	96.5	32.4
Wintrobe,[4] Baltimore	86 men	16.00	47.0	5.48	29.1	85.7	34.0
	101 women	14.10	42.0	4.82	29.2	87.1	33.5
Mugrage and Andresen, Denver	40 men	16.54	48.35	5.42	30.5	89.2	34.2
	40 women	14.45	43.22	4.63	31.2	93.3	33.4

Wintrobe,[4] from analysis of the data obtained from a number of accurate hematologic determinations in different parts of the United States and Europe, stated that there is no significant geographic variation in values for normal blood. He obtained a general average from these values and also calculated a normal range. The limits of normal

variation which he established for the mean corpuscular hemoglobin volume and hemoglobin concentration were based on his recently reported study of [22] eighty-six men and one hundred and one women. Wintrobe's figures are compared in table 5 with those obtained in the present study.

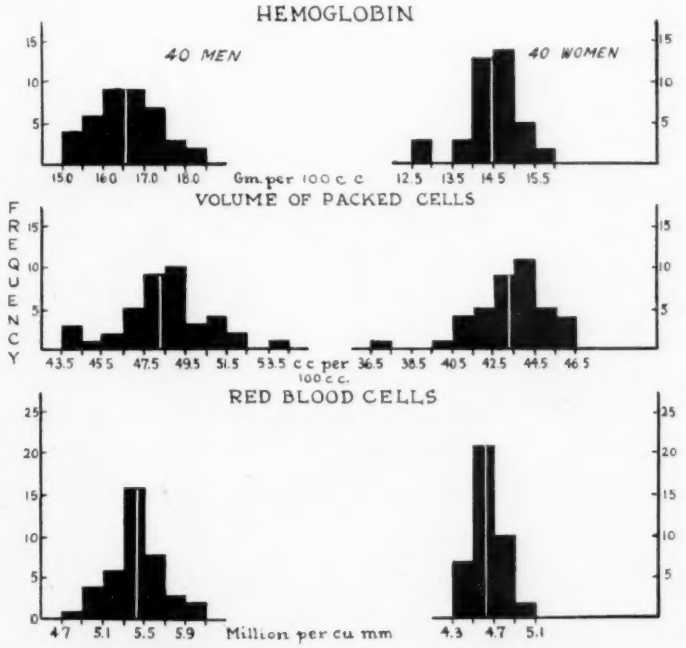

Chart 1.—Hemoglobin content, number of red blood cells and volume of packed cells in the venous blood of forty normal men (left) and of forty normal women (right). The white line indicates the arithmetic mean.

The mean hemoglobin content of the blood of the forty men was 16.54 ± 0.085 Gm. per hundred cubic centimeters; the standard deviation was 0.79 ± 0.06, and the coefficient of variation was 4.8 per cent. The mean hemoglobin content of the blood of the women was 14.45 ± 0.07; the standard deviation was 0.66 ± 0.05, and the coefficient of variation was 4.6 per cent.

The mean volume of packed cells for the blood of the forty men was 48.35 ± 0.231; the standard deviation was 2.16 ± 0.164, and the coefficient of variation was 4.4 per cent. For the blood of the forty women the mean volume of the packed cells was 43.22 ± 0.192; the standard deviation was 1.8 ± 0.136, and the coefficient of variation was 4.2 per cent.

The mean red blood cell count for the men was $5{,}420{,}000 \pm 28{,}000$; the standard deviation was 0.26 ± 0.02, and the coefficient of variation was 4.8 per cent. For the women the red cell count was $4{,}630{,}000 \pm 16{,}000$; the standard deviation was 0.15 ± 0.012, and the coefficient of variation was 3.3 per cent.

22. Wintrobe, M. M.: Anemia, Arch. Int. Med. **54**:256 (Aug.) 1934.

Tables 4 and 5 both show that values for hemoglobin and cell volume which we obtained were higher than most of those previously reported, while the number of red blood cells was higher only as compared with the averages of Haden, Walters, and Foster and Johnson. As a result, our figures for mean corpuscular hemoglobin and for mean corpuscular

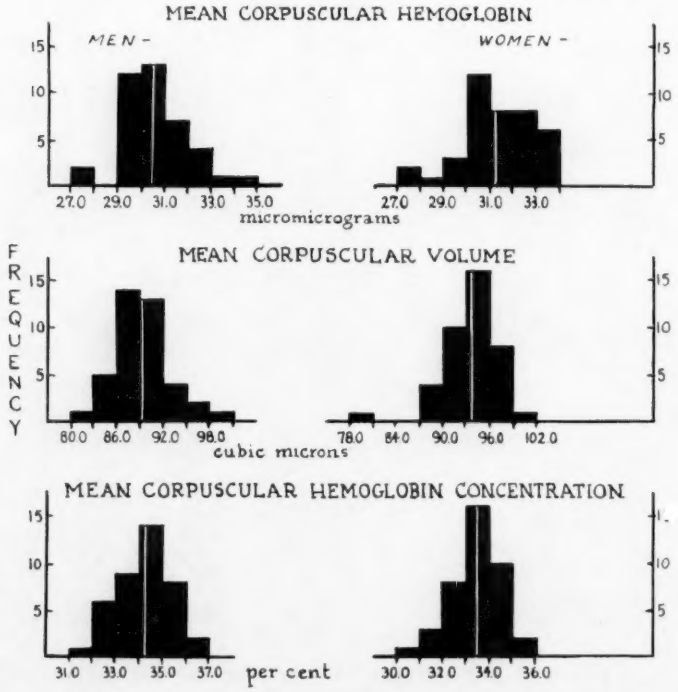

Chart 2.—The mean corpuscular hemoglobin, mean volume and mean hemoglobin concentration of the corpuscles of the venous blood of forty normal men (left) and of forty normal women (right). The white line indicates the arithmetic mean.

The mean corpuscular hemoglobin for the men was 30.5 micromicrograms ± 0.15; the standard deviation was 1.4 ± 0.1, and the coefficient of variation was 4.5 per cent. For women, the mean corpuscular hemoglobin was 31.2 ± 0.16 micromicrograms, with a standard deviation of 1.5 ± 0.12 and a coefficient of variation of 4.9 per cent.

The mean corpuscular volume for men was 89.2 ± 0.38, with a standard deviation of 3.6 ± 0.27 and a coefficient of variation of 4 per cent. For women the mean corpuscular volume was 93.3 ± 0.39, with a standard deviation of 3.6 ± 0.27 and a coefficient of variation of 3.8 per cent.

The mean corpuscular hemoglobin concentration for the men was 34.2 per cent ± 0.12, with a standard deviation of 1.2 ± 0.09 and a coefficient of variation of 3.4 per cent. For the women it was 33.4 per cent ± 0.11, with a standard deviation of 1.1 ± 0.08 and a coefficient of variation of 3.2 per cent.

volume were higher than the general averages given by Wintrobe, with many of the individual values considerably above his upper limits of normal. The volume of the individual corpuscles of the women of our series was significantly greater than that of the men. A similar difference between the red blood cells of the two sexes was noted by Osgood and Haskins [2b] in their series.

Our average of 91.2 cubic microns for the two sexes falls about midway between Wintrobe's general average of 86.7 and Hurtado's

TABLE 5.—*Comparison of the Data Obtained by Wintrobe with Those from the Present Study*

	Men				Women			
	Mean	Range*	Maximum	Minimum	Mean	Range*	Maximum	Minimum
Red blood cells								
Wintrobe,[4]	5.4	4.6 to 6.2			4.8	4.2 to 5.4		
Mugrage and Andresen	5.42	5.16 to 5.68 (in 72.5%)	4.83	6.07	4.63	4.48 to 4.78 (in 80%)	4.41	5.00
Hemoglobin								
Wintrobe,[4]	16.0	14.0 to 18.0			14.0	12.0 to 16.0		
Mugrage and Andresen	16.54	15.7 to 17.3 (in 67.5%)	15.0	18.3	14.45	13.8 to 15.1 (in 72.5%)	12.7	15.7
Volume of packed cells								
Wintrobe,[4]	47.0	40.0 to 54.0			42.0	37.0 to 47.0		
Mugrage and Andresen	48.35	46.1 to 50.5 (in 70%)	43.8	53.6	43.22	41.4 to 45.0 (in 72.5%)	37.1	46.1
Mean corpuscular volume								
Wintrobe,[22]	86.5	82.0 to 92.0 (in 85%)			87.0	82.0 to 92.0 (in 85%)		
Mugrage and Andresen	89.2	85.6 to 92.8 (in 77.5%)	81.3	99.6	93.3	89.7 to 96.9 (in 80%)	79.4	99.5
Mean corpuscular hemoglobin								
Wintrobe,[22]	29.2	27.0 to 31.0 (in 88%)			28.8	27.0 to 31.0 (in 88%)		
Mugrage and Andresen	30.5	29.1 to 31.9 (in 77.5%)	27.2	34.0	31.2	29.7 to 32.7 (in 77.5%)	27.1	33.9
Mean corpuscular hemoglobin concentration								
Wintrobe,[22]	33.7	32.0 to 36.0 (in 86%)			33.4	32.0 to 36.0 (in 86%)		
Mugrage and Andresen	34.2	33.0 to 35.4 (in 67.5%)	31.9	56.8	33.4	32.3 to 34.5 (in 80%)	30.9	35.5

* Figures for our series represent the limits of plus and minus one standard deviation from the mean and the percentage of individuals falling within these limits.

figure of 96.2 cubic microns for persons living in high altitudes. However, when one takes into account the reports given in table 4 one notes that Haden's average of 91.7 cubic microns for both sexes is a little higher than ours. Foster and Johnson's figure of 88.7 cubic microns for men at New Orleans is only slightly lower than our value of 89.2 for men. The difference between the corpuscular volume in our series and that given by Wintrobe as the world average cannot be explained, therefore, on the basis of the effect of altitude. It seems to suggest at least a variation in the corpuscular volume, which may require the use of regional standards.

Our figures for mean corpuscular hemoglobin concentration are almost identical with Wintrobe's general average and with most of the values previously reported. Further confirmation is given to previous observations that the value for this factor is remarkably constant in the blood of normal persons.

SUMMARY

Previous reports of values for the hemoglobin content, the volume of packed cells and the number of red blood cells of the venous blood of normal adults have been made almost entirely from regions not more than 1,000 feet (304 meters) above sea level.

Information regarding the venous blood of forty normal white men and of an equal number of normal white women living at an altitude of about 5,000 feet (1,520 meters) is given in the present study. Determinations of the number of red blood cells, the volume of packed cells and the amount of hemoglobin, figured from the oxygen capacity, are reported for two hundred and forty samples. Corpuscular constants obtained from these values are discussed. The close agreement between the average values for hemoglobin obtained by three methods is shown.

The mean value for hemoglobin of 16.54 Gm. per hundred cubic centimeters of blood for men and 14.45 Gm. for women and also the mean packed cell volume of 48.35 cc. per hundred cubic centimeters of blood for men and 43.22 cc. for women are somewhat higher than values generally reported in other parts of the country. The mean red blood cell counts of 5,420,000 per cubic millimeter for men and 4,630,000 for women are about the same as the general average compiled by Wintrobe.

The value for mean corpuscular hemoglobin of 30.5 micromicrograms for men and 31.2 micromicrograms for women as well as the mean corpuscular volume of 89.2 cubic microns for men and 93.3 cubic microns for women are higher than Wintrobe's general average.

Figures for mean corpuscular hemoglobin concentration of 34.2 per cent for men and 33.4 per cent for women further confirm previous observations of its constant value in normal human blood.

PRIMARY IDIOPATHIC THROMBOPHLEBITIS

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Thrombophlebitis may occur as a primary disease in healthy, active persons who otherwise are normal. In a series of one thousand and eleven unselected consecutive patients with thrombophlebitis of all types seen at the Mayo Clinic in a five year period, seventy-nine formed the basis for the study under discussion. The patients had no evidence of constitutional disease, such as carcinoma or arthritis. They had not undergone surgical operation or childbirth recently and had not recently had a specific infectious disease. They did not have recognizable disease of the heart or dyscrasia of the blood. There was no history or evidence of gross mechanical trauma or of local infectious or suppurative processes in the region of the veins. The patients had not had previous disease of the veins, such as varix. They were examined carefully for occlusive disease of the peripheral arteries, but this was not found. In other words, known causes of thrombophlebitis and conditions in which thrombophlebitis is sometimes seen as a complication were not present, and there was no recognizable factor of abnormal venous stasis.

HISTORY

In 1845 Jadioux [1] reported a case in which thrombophlebitis of the left femoral vein affected an otherwise healthy man aged 20. It occurred in three separate episodes in four months, without fever or other constitutional disturbance. In 1864 Frémy [2] reported a case in which thrombophlebitis affected an otherwise healthy man of 56. It apparently involved the popliteal and the long saphenous vein of the left leg in a series of episodes. Sir James Paget [3] wrote in 1866 that there was a type of thrombophlebitis not associated with trauma, exhaustion, infectious disease, local inflammation, pyemia, puerperium or varicosity, which affected patients who had gout but also affected patients with "gouty inheritance" who did not have clinical gout. He described frequent recurrences, mainly in the lower limbs, affecting the superficial rather than the deep veins, and said that the lesions appeared to migrate or jump from one vein to another and usually involved both legs. He

From the Division of Medicine, the Mayo Clinic.

1. Jadioux, quoted by Briggs.[5]
2. Frémy, quoted by Briggs.[5]
3. Paget, James: On Gouty and Some Other Forms of Phlebitis, St. Barth. Hosp. Rep. **2**:82, 1866.

noted that the affected superficial veins were palpable and hard, that occasionally the deep femoral vein also was involved and that the attacks were accompanied by only slight fever or constitutional disturbances. He observed that some veins subsequently became pervious while others were permanently obstructed. He described the development of collateral veins in some cases and stated that pulmonary embolism was rare according to his experience, since he had observed only three cases of nonfatal embolism, in one of which fatal embolism subsequently occurred.

A similar syndrome was described in 1894 by Daguillon,[4] who reported five cases and reviewed seven others. He expressed the belief that the disease was the result of a diathetic influence, an arthritic but nongouty constitution. He found a high incidence of pulmonary embolism, which was present in six of the twelve patients, three of whom died. In 1905 Briggs [5] stated that there was a disease which had to be classified as "idiopathic recurrent thrombophlebitis," and he cast considerable doubt on the gouty or arthritic origin in the cases reported by Paget and Daguillon. He expressed the opinion that the condition primarily was phlebosclerosis resulting from an anatomic constitutional fault. Subsequently a number of such cases have been reported as instances of "phlebitis migrans" or "thrombophlebitis migrans." This term, for the two may be considered as one, is a rather good descriptive name but has no etiologic significance as it has been applied to a number of secondary as well as primary types of recurrent peripheral and visceral phlebitis. It has never had a clearcut definition. The term was first used by Neisser [6] in 1903 to describe a type of superficial phlebitis occurring in syphilis. Schwarz [7] in 1905 described two cases of phlebitis migrans (nonsyphilitic) in which the condition was associated with advanced tuberculosis. Buerger [8] in 1909 emphasized the association of thrombophlebitis migrans and thrombo-angiitis obliterans and the necessity for examining patients who have thrombophlebitis migrans for existent evidence of arterial disease and of watching for future development of arterial lesions. Herrick [9] in 1911 described a

4. Daguillon, quoted by Briggs.[5]

5. Briggs, J. B.: Recurring Phlebitis of Obscure Origin, Bull. Johns Hopkins Hosp. **16**:228 (June) 1905.

6. Neisser, Ernst: Ueber wandernde Phlebitis, Deutsche med. Wchnschr. **29**: 660 (Sept. 10) 1903.

7. Schwarz, Gottfried: Phlebitis migrans (nonsyphilitica), Virchows Arch. f. path. Anat. **182**:178, 1905.

8. Buerger, Leo: The Association of Migrating Thrombophlebitis with Thrombo-Angeitis Obliterans, Internat. Clin. **3**:84, 1909.

9. Herrick, W. W.: Phlebitis Migrans, with Report of a Case, Am. J. M. Sc. **142**:874 (Dec.) 1911.

case of phlebitis migrans in which the venous lesions apparently were not associated with any other disease. He thought that it was the result of some unknown toxin and that there was no danger of embolism. He believed there was no thrombosis, but merely periphlebitis.

Since 1911 cases of thrombophlebitis migrans in which the venous lesion was not associated with arterial involvement, preexisting varix, infection or systemic diseases have been reported by Harkavy,[10] Chlumský,[11] Johnson,[12] Moorhead and Abrahamson,[13] Ryle,[14] Collier,[15] Barber,[16] Walker,[17] Hartfall and Armitage,[18] Krieg [19] and others. The largest series was reported by Kletz [20] and consisted of five cases.

Associated with the venous lesions of the extremities, Harkavy reported involvement of the portal vein; Moorhead and Abrahamson, involvement of the cerebral and mesenteric veins; Ryle, and Hartfall and Armitage, mesenteric and pulmonary infarcts; Barber and Walker, cerebral lesions. The diagnosis in these cases was based on clinical findings and was unproved. Ryle felt that the pulmonary infarcts were the result of local thrombophlebitis of the pulmonary veins and were not caused by embolism.

With regard to etiologic factors in idiopathic recurrent or migratory thrombophlebitis, in addition to the uricogenic theory of Paget and Daguillon's theory of arthritic diathesis, Briggs', of phlebosclerosis and Herrick's, of toxin, Owen [21] stated that the condition was caused by influenza or associated with influenzal epidemics. Ryle, Kletz, and Hartfall and Armitage noted associated foci of infection and cessation

10. Harkavy, Joseph: Phlebitis and Thrombophlebitis Migrans, M. J. & Rec. **120**:64 (July 16) 1924.

11. Chlumský, V.: Ueber Phlebitis chronica migrans, Zentralbl. f. Chir. **54**: 75 (Jan. 8) 1927.

12. Johnson, W. R.: Recurrent Idiopathic Superficial Phlebitis: Its Significance in Adult Men, M. Clin. North America **2**:1559 (May) 1928.

13. Moorhead, T. G., and Abrahamson, Leonard: Thrombo-Phlebitis Migrans, Brit. M. J. **1**:586 (April 7) 1928.

14. Ryle, J. A.: Thrombo-Phlebitis Migrans, Lancet **2**:731 (Oct. 4) 1930.

15. Collier, W. T.: Thrombo-Phlebitis Migrans, Involving the Deep Veins of All Four Limbs, Lancet **2**:1408 (Dec. 26) 1931.

16. Barber, Hugh: A Case of Thrombo-Phlebitis Migrans, Brit. M. J. **1**: 281 (Feb. 13) 1932.

17. Walker, A. B.: Observations on Thrombo-Phlebitis Migrans with Notes of a Case, Lancet **2**:936 (Oct. 29) 1932.

18. Hartfall, S. J., and Armitage, George: Thrombo-Phlebitis Migrans: A Report of Two Cases, Guy's Hosp. Rep. **82**:424 (July-Oct.) 1932.

19. Krieg, E.: Thrombophlebitis migrans peripherer Venen, München. med. Wchnschr. **79**:1712 (Oct. 21) 1932.

20. Kletz, Norman: Thrombo-Phlebitis Migrans, Lancet **2**:938 (Oct. 29) 1932.

21. Owen, A. W.: Thrombo-Phlebitis Migrans, Brit. M. J. **1**:690 (April 21) 1928.

of attacks after their removal. Harkavy [22] found that the skin was sensitive to extracts of tobacco in two of five cases. In the majority of the reported cases the patient was a young or middle-aged man.

Reports of cases in which primary idiopathic thrombophlebitis occurred as a single episode and affected chiefly the large veins, such as the iliac, femoral, or saphenous vein, are rare in the literature. Such a case, in which death occurred, was reported by Hutchinson [23] in 1850. Another case, in which there was involvement of the right iliac, femoral and popliteal vein, was reported by Dowse [24] in 1879. The patient was obese, and the outcome was fatal. The clinical diagnosis was confirmed at necropsy. Mueller [25] in 1929 reported observations made in a case of idiopathic thrombophlebitis of the femoral vein ten years after the lesion had occurred. During the interval there had been no episodes of thrombophlebitis.

The seventy-nine cases which form the basis for this study are arbitrarily divided into two groups: (1) forty cases in which the thrombophlebitis was of the recurrent type and was similar to that in certain cases reported as instances of thrombophlebitis migrans in which there was no associated disease, and (2) thirty-nine cases in which there was only a single episode of thrombophlebitis.

These two groups will be considered separately as they present certain clinical differences. It is possible that some of the patients who had a single episode of thrombophlebitis will have recurrences in the future, and it is recognized that the interval between episodes in some cases of the recurrent type is rather long.

RECURRENT IDIOPATHIC THROMBOPHLEBITIS

Age at the Onset of the Disease.—The youngest patient was 21 and the oldest 67 years of age. The average age was 40, and 80 per cent of the patients were less than 50. The incidence by decades was as follows: Seven patients were between 20 and 29 years of age; thirteen, between 30 and 39; twelve, between 40 and 49; five, between 50 and 59, and three, between 60 and 69.

Sex.—Thirty-five patients (88 per cent) were men.

Race.—The distribution according to race was as follows: Nineteen patients were English, Irish, Scotch or Welsh; ten were German; five were Jewish; three

22. Harkavy, Joseph: Tobacco Sensitiveness in Thromboangiitis Obliterans, Migrating Phlebitis and Coronary Artery Disease, Bull. New York Acad. Med. **9**:318 (May) 1933.

23. Hutchinson, D.: Crural Phlebitis Occurring in the Male, Northwest M. & S. J. **7**:339, 1850-1851.

24. Dowse, T. S.: Note of a Case of Thrombosis with Remarks, Lancet **2**: 268 (Aug. 23) 1879.

25. Mueller, Robert: Thrombosis of Venous System: Late Physical Effects and Symptomatology with Special Reference to Lower Extremities, J. Missouri M. A. **26**:65 (Feb.) 1929.

were Scandinavian; two were French, and one was Dutch. The proportion of Jewish patients (12 per cent) who had this type of thrombophlebitis was a little higher than the percentage of Jewish patients who register at the clinic.

Occupation.—This was classed as sedentary in twenty-four cases and as active in sixteen.

History.—Twenty-five patients gave a history of one or more major acute infectious diseases, but none had had thrombophlebitis as a complication or sequela of these diseases.

Number and Frequency of Episodes.—At the time of their first examination, sixteen patients had had thrombophlebitis for less than a year and nine for more than five years. Twenty-one patients said that they had had episodes at intervals of from a few days to a month, and in some attacks several veins had been affected at one time. Nineteen patients had had more definite single episodes at intervals of from six weeks to four years. One patient had had twenty to thirty such attacks in eighteen years. Five had had only two attacks.

Site and Nature of the Lesions.—The veins of both legs were involved in twenty-seven cases, those of the right leg alone in nine cases, those of the left

Incidence of Involvement of Various Veins in Forty Cases of Recurrent Idiopathic Thrombophlebitis

	Involved at Some Time	Involved Primarily	No Other Veins Involved
Superficial veins of leg	22	12	4
Long saphenous vein	28	15	6
Short saphenous vein	14	8	1
Popliteal vein	5	1	..
Femoral vein	12	3	1
Iliac vein	2	..	..
Superficial veins of arm	4	..	..
Median basilic vein	1	1	..
Superficial veins of abdomen	3	..	..
Superficial veins of scrotum	1	..	..

leg alone in three cases and those of the right arm alone in one case. The frequency of involvement of the various veins is shown in the table. The superficial veins of the legs were affected alone in four cases, the long saphenous vein alone in six cases, the short saphenous vein alone in one case and the femoral and iliac veins in one case. The femoral vein was primarily involved in only two other cases. In twenty-eight cases small, medium and large veins in various combinations were affected. Evidence of intra-abdominal thrombophlebitis was present in only one case; the condition was progressive and proved fatal. The patient had an attack of severe abdominal pain and melena. Roentgenologic examination of the gastro-intestinal tract did not reveal anything abnormal, and it was assumed but not proved that the patient had mesenteric thrombophlebitis.

The lesions of the superficial and the saphenous veins appeared to be definitely inflammatory in all cases. There were moderate local pain and usually considerable local tenderness during the acute stage. The veins could be felt as firm, indurated cords, and there was visible local rubor. The acute stage lasted for from one to six weeks, during which time most of the patients were at least partially disabled as walking aggravated the pain. The cordlike vein usually could be felt for several weeks after the acute attack. The involved regions were definitely segmental and varied in length from a few millimeters in the superficial veins and a few centimeters in the saphenous veins (fig. 1 *A*) to the entire extent, from groin

to ankle, of the long saphenous vein. In four cases the lesions slowly ascended the long saphenous vein, new segments a few centimeters in length being involved one at a time over a period of months. Constitutional symptoms were slight or absent in all but six cases. Five patients had mild fever, with a temperature from 99 to 101 F., and malaise. In the case in which the mesenteric veins were involved there was prolonged fever, the temperature being as high as 103 F., and much prostration, and later severe anemia developed. The patient died, apparently from generalized toxemia.

Pulmonary Embolism and Infarction.—Acute infarctions of the lung occurred in twelve cases (30 per cent). One of the patients had three episodes, three had two episodes and the other eight had only one episode. Of the seventeen pulmonary infarctions, seven occurred at the onset of clinical thrombophlebitis of the femoral vein, three at the onset of thrombophlebitis of the long saphenous vein, one at the onset of thrombophlebitis of the short saphenous vein, one a week after the onset of thrombophlebitis of the long saphenous vein and one a week after the onset of thrombophlebitis of the short saphenous vein. The other four infarctions occurred two, four, four and six weeks, respectively, after episodes of thrombophlebitis of the femoral vein. Two patients died, with the clinical picture of pulmonary embolism. Each had had two previous episodes of pulmonary infarction. Necropsy was not performed in these cases.

Focal Infection.—Definite foci of infection were present in thirty-one cases (77 per cent); no foci were found in seven, and no data were available in two. Some patients had more than one focus. The foci originated in infected tonsils in nineteen cases, in infected teeth in eighteen cases, in chronic prostatitis in eight cases, in chronic cervicitis in two cases and in chronic suppurative otitis media in one case.

Obesity.—Obesity was present in eleven cases (27 per cent).

Hypertension.—Hypertension of from mild to moderate degree was present in three cases.

Special Hematologic Studies.—As has been indicated, routine studies of the blood, such as estimation of the amount of hemoglobin, enumeration of erythrocytes and leukocytes and the Wassermann or the Kline test, were made in all cases but did not reveal anything abnormal. In a number of cases a differential blood count, estimation of the coagulation time (Lee's method), enumeration of the blood platelets, estimation of the bleeding time and determination of the sedimentation rate were made both in the course of acute episodes and between episodes. These tests also failed to disclose any abnormality. The plasma coagulability index (Nygaard method)[26] was determined in eleven cases. In eight cases it was normal, and in three it was definitely increased. The clinical significance of this test has not been established as yet, but these data are inserted for purposes of record.

Local Complications of the Thrombophlebitis.—Persistent edema of an affected leg (fig. 1 *B*) occurred in nineteen cases. This was of mild degree in nine and of moderate degree in ten cases. It occurred in six of nine cases in which obesity was present, in eleven of twelve cases in which the femoral vein was involved, in only two cases in which both saphenous veins were involved, in two of six cases in which the long saphenous vein was involved and in two of five cases in which the short saphenous vein was involved. Secondary varicose veins developed

26. Nygaard, K. K.: Coagulability of Blood Plasma, Proc. Staff Meet., Mayo Clin. **7**:544 (Sept. 21) 1932.

in eleven cases, and ulcers caused by stasis occurred later in four of these. Three patients had pigmentation, and one had dermatitis caused by stasis. Persistent pain in the region of the inflamed veins occurred in nine cases. A definite neurosis developed in three.

Pathology and Bacteriology.—Portions of acutely involved veins were removed or the entire venous lesion was excised under local anesthesia in eleven of the forty cases. In eight cases these specimens, which were from 1 to 4 mm. in diameter, were obtained from the superficial veins of the lower part of the leg.

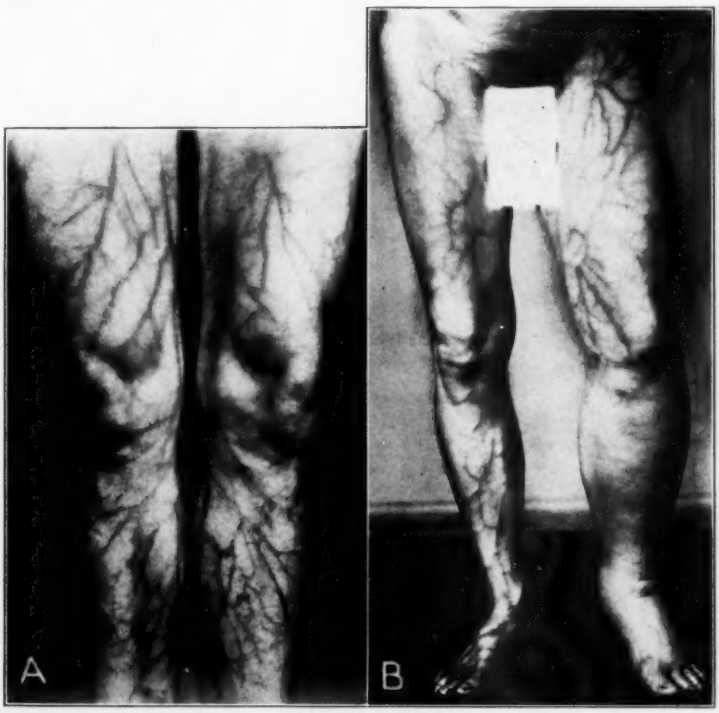

Fig. 1.—*A*, infra-red photograph showing recurrent idiopathic thrombophlebitis in one of its most common sites, namely, the left long saphenous vein in the lower third of the thigh. The periphlebitis appears as a dark strip with poorly defined markings. The long saphenous vein and its tributaries in the left calf are abnormally prominent as a result of an increase in pressure caused by proximal obstruction. There is no edema. *B*, infra-red photograph showing recurrent idiopathic thrombophlebitis which has involved successively the superficial long saphenous, the femoral and the iliac vein of the left leg, with resultant chronic venous insufficiency and marked edema. The superficial veins of the left thigh are abnormally prominent and distended.

In two cases a portion of the long saphenous vein and in another case a portion of the median basilic vein of the arm was excised. A culture was made from a part of each lesion by Dr. T. B. Magath and Dr. Luther Thompson in the following manner: The material was placed in a sterile Petri dish and was then ground in sterile water with sterile sand and a small amount of physiologic solution of sodium chloride. Portions of this solution were placed in tubes of brain broth, some of which were covered with sterile petrolatum. Other portions were put on blood agar plates and incubated both aerobically and anaerobically. Some of the solution was distributed on dextrose-tartaric agar plates and on Sabouraud's culture medium. All the cultures were held for a minimum of one week, and some for three weeks, before being discarded. They were uniformly sterile.

The remainder of the lesions were fixed in a dilute solution of formaldehyde U. S. P. (1:10), embedded in paraffin, cut in sections 7 microns thick and stained

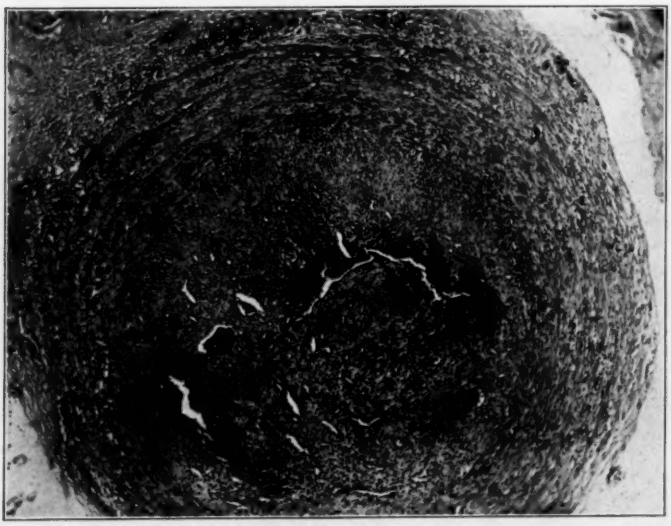

Fig. 2.—Photomicrograph (× 40) of a section of a superficial vein excised in an acute stage of recurrent idiopathic thrombophlebitis and stained with hematoxylin and eosin. Complete occlusion of the lumen by a cellular thrombus is shown. There is marked infiltration of the wall of the vein and of the perivenous tissue by connective tissue cells.

with hematoxylin and eosin, Van Gieson's stain, and elastin H or Weigert's elastic tissue stain. In all cases the lumens of the veins were occluded. In nine cases the pathologic picture was similar (figs. 2, 3 and 4); that is, the occluding mass was made up of well organized tissue, which in some cases contained a few collections of erythrocytes but consisted mainly of connective tissue cells of various types. There were a few lymphocytes, and neutrophilic and eosinophilic leukocytes occasionally were found. In most cases the mass contained a few minute clefts or canals lined with endothelium. The internal elastic lamina was often thickened and partially disrupted. The medial coat of the vein was fairly well preserved but contained a number of small vacuoles. It was heavily infiltrated

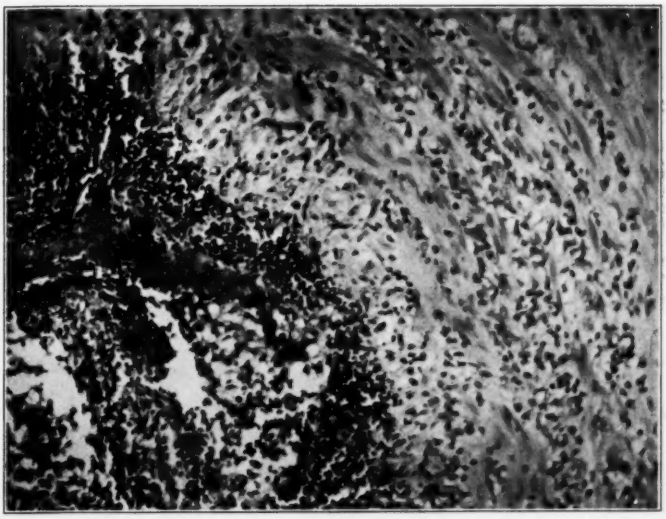

Fig. 3.—Photomicrograph (× 170) of a section of a superficial vein excised in an acute stage of recurrent idiopathic thrombophlebitis and stained with hematoxylin and eosin. The giant cells in the organizing thrombus, the marked proliferation of the intima and the infiltration of the media may be noted.

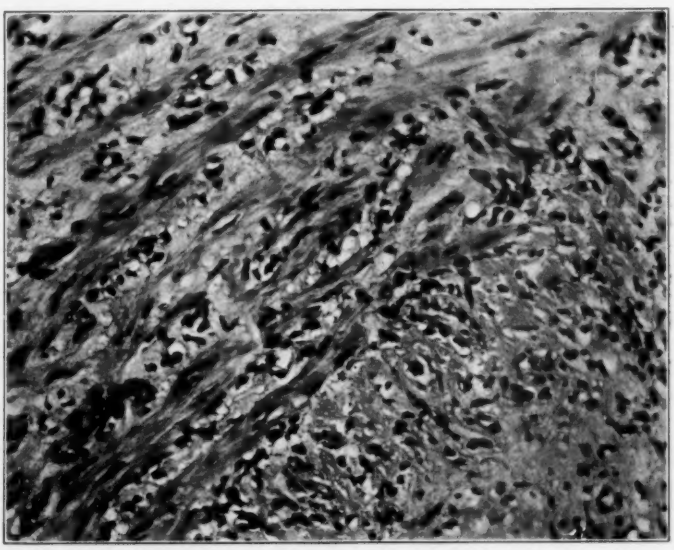

Fig. 4.—Photomicrograph (× 250) of a section of a superficial vein excised in an acute stage of recurrent idiopathic thrombophlebitis and stained with hematoxylin and eosin. The various types of connective tissue cells and fibroblasts in the organized thrombus and wall of the vein are shown, as well as the edema and vacuolation of the medial coat.

with connective tissue cells and fibroblasts of various types. The adventitia was similarly infiltrated, and often the infiltrating cells extended a considerable distance into the fatty perivenous tissue. Many of the vasa vasorum were surrounded by lymphocytes and fibroblasts. In three cases giant cells were found in the occluding mass. In two cases the entire pathologic picture was somewhat different and showed only a partially organized red thrombus and considerably less infiltration of the media and adventitia with connective tissue cells than was present in the other cases.

This pathologic picture of a vein heavily infiltrated with connective tissue cells and occluded by a cellular mass of connective tissue which sometimes contains giant cells is essentially indistinguishable from the pathologic picture of thrombo-angiitis obliterans, except possibly in degree of reaction. Affected veins in typical thrombo-angiitis obliterans occasionally are the sites of more dense infiltration with connective tissue cells than those observed in recurrent idiopathic thrombophlebitis.

IDIOPATHIC THROMBOPHLEBITIS OCCURRING IN SINGLE EPISODES

Age.—The youngest patient was 20 and the oldest 69 years of age. The average age was 43. The age distribution by decades was fairly even. Seven patients were between 20 and 29 years old; eight, between 30 and 39; ten, between 40 and 49; eight, between 50 and 59, and six, between 60 and 69.

Sex.—Twenty-four patients (62 per cent) were men.

Race.—The distribution according to race was as follows: Twenty-three patients were English, Irish, Scotch or Welsh; seven were German; four were Scandinavian; two were Dutch; one was Italian; one was Slavic, and one was Jewish.

Occupation.—The occupations of twenty-nine patients (74 per cent) were considered active.

History.—Twenty-eight patients (70 per cent) gave a history of major infectious diseases, but none of these had had thrombophlebitis as a complication.

Site and Nature of the Lesion.—Both legs were affected simultaneously in three cases; the right leg was involved in nine cases, and the left leg, in twenty-seven cases. The veins affected were as follows: the femoral vein in eighteen cases, the femoral and iliac veins in seven cases, the long saphenous vein in eight cases, the popliteal vein in three cases, the short saphenous vein in two cases and the external jugular vein in one case. Systemic reactions in all these cases were relatively slight. In fourteen cases there was fever, but the temperature was less than 101 F. There were no chills. In the cases in which the saphenous vein was involved the lesion occurred in long segments only and was associated with moderate pain and tenderness in the vein and slight to moderate evidence of periphlebitis. The clinical picture in the cases in which there was involvement of the femoral and iliac veins was in no way different from that seen in cases of secondary thrombophlebitis in which the same veins are affected.

Pulmonary Infarction.—This occurred in only three cases and in each at the onset of the thrombophlebitis. The site of the thrombophlebitis was in the femoral vein in one case, in the long saphenous vein in another and in the popliteal vein in the third. Fatal pulmonary embolism did not occur in any of these cases.

Foci of Infection.—These were present in twenty-two cases but were not found in eleven. The data were incomplete in six cases. The foci originated in

infected tonsils in thirteen cases, in infected teeth in seven cases, in chronic prostatitis in three cases, in chronic cervicitis in two cases and in chronic paranasal sinusitis in one case.

Obesity.—This was present in a rather large number of cases (eighteen, or 46 per cent).

Hypertension.—In eight cases definite elevation of blood pressure was found.

Local Complications of the Thrombophlebitis.—Persistent edema of varying degree occurred in thirty cases. It occurred in all but one of those in which the femoral or iliac vein was involved, in half of those in which the long saphenous vein was involved and in two of three cases in which the popliteal vein was involved. Secondary varicose veins developed in ten cases. In three of these stasis caused ulcers; in four, eczema, and in one, pigmentation. Persistent pain occurred in ten cases. In seven of these it was at the site of the thrombophlebitis; in two it occurred in the muscles of the calf while the patient was walking, and in one it consisted of noctural cramps. Chronic indurative cellulitis developed in one case, osteoporosis of the bones of the foot (partly at least from disuse) in another and a definite neurosis in a third. Biopsy was not performed in these cases.

COMMENT

The arbitrary division of these cases of idiopathic thrombophlebitis into two groups according to whether there were multiple episodes or only one is open to question, and it is possible that some of the patients who have had a single episode may have recurrences. However, twenty (more than half) of these patients have been observed for a year and seven for at least five years without recurrences. Only seven of the patients who had recurrent thrombophlebitis had freedom between episodes for as long as a year. There were certain other differences between the two groups. The patients who had single episodes did not reveal any striking similarities as to age, sex or occupation, but did reveal a rather high incidence of obesity. In this group there was rather extensive thrombophlebitis, usually of large venous trunks and less frequently of medium-sized veins. In these respects nonrecurrent idiopathic thrombophlebitis resembles the secondary or complicating types.

The term thrombophlebitis migrans is not used in this paper, as it has been used too loosely in the literature. It is felt that recurrent idiopathic thrombophlebitis, the term used by Briggs, limits the described cases to a definite group and emphasizes the primary character of the venous lesion. Recurrent idiopathic thrombophlebitis is predominantly, although not exclusively, a disease of young and middle-aged men. It is essentially and primarily a disease of small and medium-sized veins. The lesions tend to occur in short segments and appear to be definitely inflammatory. These observations suggest an analogy to thrombo-angiitis obliterans, which also is a disease of young and middle-aged men, involves short segments of the vessels and has a definite tendency to recur in episodes. Thrombo-angiitis obliterans, however, involves

chiefly arteries, although sometimes it attacks both arteries and veins. It has been mentioned (by Buerger and by Johnson) that the arterial lesions of thrombo-angiitis obliterans may develop in cases of migrating superficial thrombophlebitis, and it is possible that some of the patients in the group whose cases are analyzed in this paper may have had early thrombo-angiitis without arterial lesions. However, it seems certain that arterial lesions which can be recognized clinically do not develop in most cases of recurrent idiopathic thrombophlebitis. It is not illogical to consider recurrent idiopathic thrombophlebitis as a type of thrombo-angiitis obliterans which inovlves only the veins, just as another type involves only the arteries in certain cases (60 per cent). Thrombo-angiitis obliterans, although a definite clinical and pathologic entity, is still an etiologic puzzle. Recurrent idiopathic thrombophlebitis does show some differences from typical thrombo-angiitis obliterans with involvement of the veins. The limitations as to age and sex are not so sharp. There is some tendency for recurrent thrombophlebitis to involve large veins (femoral and iliac in 33 per cent of the cases). These veins rarely are involved in thrombo-angiitis. Pathologically, there is slightly less proliferation of connective tissue in recurrent idiopathic thrombophlebitis than there is in thrombo-angiitis. These may be hair-splitting distinctions.

Like the secondary types of thrombophlebitis, the idiopathic type still presents an unsolved problem in pathogenesis. It reopens the old question of primary phlebitis versus primary thrombosis. In the recurrent types the local inflammatory reaction and the predilection of the lesion for segments of superficial veins are strongly suggestive of a primary lesion of the wall of the vein. However, an increase in tendency to thrombosis might be a contributing factor. A reasonable hypothesis seems to be that the lesions in the veins occur as the result of hypersusceptibility of the venous tissue to injury by toxins or viruses or as the result of the elective localization or affinity of certain toxins or viruses for the venous tissues. There was a rather high incidence of focal infection in the patients observed, and there were certain analogies to other recurrent diseases considered of focal origin.

The question as to whether the pulmonary infarctions are caused by small emboli or localized pulmonary thrombophlebitis cannot be answered definitely without adequate pathologic studies. In the present series evidence of visceral lesions elsewhere than in the lungs was rare. The occurrence of pulmonary infarcts at the onset of the thrombophlebitis, particularly of the large veins, is compatible with the present conception of the occurrence of embolism, namely, that it breaks off when the thrombus is new and before it has had a chance to become organized. Pulmonary infarctions which follow thrombophlebitis that

has been present for several days or weeks may represent the breaking off of a newly propagated thrombus into a larger vein. I feel that the evidence indicates that these infarctions are caused by emboli.

The recognition of idiopathic thrombophlebitis as a cause of transient and prolonged disability and occasionally of death, as well as recognition of its unsolved problems, should be a stimulus to further investigations regarding its cause and pathogenesis.

SUMMARY

Idiopathic or primary thrombophlebitis is a definite clinical entity. A study of seventy-nine cases shows that there are two types: First, a recurrent segmental inflammatory venous lesion which tends to involve chiefly small and medium-sized veins and occurs most commonly among young and middle-aged males; second, thrombophlebitis of medium-sized and large veins which is accompanied by less inflammation than is the former lesion and occurs as a single episode without particular preponderance as to age or sex. Recurrent idiopathic thrombophlebitis histopathologically is similar to thrombo-angiitis obliterans. Cultures of segments of affected veins which have been obtained for biopsy have shown nothing abnormal. The patients in the series of cases studied revealed a high incidence of definite focal infection in tonsils, teeth and prostate gland. Pulmonary infarction occurred in 30 per cent and fatal pulmonary embolism in 5 per cent. Chronic venous insufficiency of a limb occurred in approximately half of the patients with recurrent and in two thirds of the patients with nonrecurrent thrombophlebitis.

Progress in Internal Medicine

TREATMENT OF POSTOPERATIVE PARATHYROID INSUFFICIENCY

AN INTERPRETATIVE REVIEW OF THE LITERATURE

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The present paper is limited to a review of the constructive literature which is pertinent to the understanding of the physiologic function of the parathyroid glands, so that patients who have unavoidably suffered injury or destruction of the glands as a result of operation on the thyroid gland may be successfully and satisfactorily treated. The literature on the experimental side is so extensive that only the most important constructive articles can be referred to, and it seems unnecessary to cite more than a few of the early reports, which are of a negative or conflicting nature. Several previous reviews cover the controversial points of these investigations in considerable detail.

The parathyroid glands were first described and named as distinct anatomic entities by Sandström in 1880, although, as he pointed out, both Remak (1851) and Virchow (1864) had previously seen and briefly described them in connection with the thyroid gland.

Weiss, in a report in 1881 of the results of thyroidectomy at Billroth's clinic, mentioned tetany as a serious postoperative complication, as did Reverdin (1882) and Kocher (1883). The symptom complex, which Kocher termed "cachexia strumipriva," was as a rule the result not only of thyroid but of parathyroid deficiency. Schiff (1884) demonstrated that after complete removal of the thyroid gland of dogs and cats the animal usually died of spastic or fibrillary contraction and tetany; these experimental observations were confirmed by Wagner (1884), Carle (1888), von Eiselsberg (1890) and others.

However, it was not until 1891 that Gley demonstrated that the tetany which follows thyroidectomy did not occur unless the *glandules thyroïdiennes*, as he preferred to call the parathyroid bodies described by Sandström, also were removed. However, as removal of all visible

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parathyroid tissue did not cause fatal tetany in his experimental animals, he was by no means certain that the parathyroid glands were complete physiologic entities. His experimental results were soon confirmed by Verstraeten and Vanderlinden (1894). Vassale and Generali were the first (1896) to show definitely that the removal of all parathyroid tissue, even with the preservation of thyroid tissue, led to fatal tetany, while no tetany resulted if one of the four parathyroid glands remained intact and was capable of functioning; they therefore concluded that the parathyroid glands are not in any way related to the thyroid gland but are special organs possessing a metabolic function of their own, which in some way, still unknown, prevents tetany.

Erdheim, in 1906, by cauterizing the parathyroid glands confirmed the observation that tetany which follows thyroparathyroidectomy is of parathyroid and not of thyroid origin. He went still further and demonstrated that in rats which survived the tetanic convulsion a definite set of trophic disturbances invariably developed more than one month after removal of the parathyroid glands (without removal of the thyroid gland). Typical changes occurred in the incisor teeth, which became soft and elongated and either fell out or were definitely bent. The mouth and gums were the site of gangrenous stomatitis; general cachexia developed, and cataracts formed in the eyes. Erdheim demonstrated, therefore, that tetany in its acute forms is not the only disturbance produced by parathyroidectomy (with the thyroid gland intact) but that definite trophic disturbances are produced.

Thompson and Leighton (1908) exposed, crushed and ligated the parathyroid glands of dogs. Severe tetanic symptoms rarely developed as a result of this procedure, but the animals as a rule passed into a chronic condition of parathyroid insufficiency that resembled the condition which Erdheim noted in rats. This work confirmed Erdheim's suggestion that parathyroidectomy produces chronic and characteristic changes of a trophic nature in addition to, but distinct from, acute postoperative tetany. Thompson and Leighton tried to produce lesion of the parathyroid glands of the type that is likely to follow partial thyroidectomy in man. The study was suggested by Halsted, who stated: "It is in the control of hemorrhage that we sacrifice the parathyroid glandules."

The first inkling of the metabolic nature of the tetanic reaction following thyroparathyroidectomy was obtained in 1907, when Parhon and Urechie briefly reported that the intraperitoneal administration of calcium chloride somewhat ameliorates the tetany of experimental animals, although these investigators were unable to prolong the survival of the animals; they found, on the other hand, that the administration of sodium salts aggravates the symptoms.

In 1908 and 1909 MacCallum and Voegtlin demonstrated that there was a marked reduction in the amount of calcium in the serum and the brain after thyroparathyroidectomy and that this was accompanied by violent tetany, which could be completely relieved by the injection of calcium salts. The injection of magnesium salts also seemed to control the tetany, but the effects were confused by the anesthetic and toxic action of the magnesium, while the injection of salts of sodium or potassium tended to intensify the symptoms. These investigators, therefore, concluded that the parathyroid secretion in some way controls the exchange of calcium in the body and thus influences the excitability of the nerve cells. Frouin, in 1909, confirmed the results of MacCallum and Voegtlin and demonstrated that a parathyroidectomized animal could be kept alive indefinitely by continued administration of calcium salts. He emphasized the probable therapeutic value of calcium in clinical cases.

Parhon and Goldstein in 1909 stated that it is well known that a milk diet is beneficial and a meat diet harmful to thyroparathyroidectomized animals and that young animals are more susceptible to tetany than old animals. Their investigation proved that kittens survive thyroparathyroidectomy for a much longer period than usual, provided that they are nursed. The authors suggested that the kittens thereby receive the beneficial effect of a glandular secretion or that the milk so obtained destroys a poison in the gastro-intestinal tract.

Voegtlin and MacCallum (1911) confirmed their original observation that the administration of calcium salts is beneficial in parathyroid tetany, but they also found that the salts of magnesium and strontium have a beneficial effect. They stated that the salts of barium, potassium and sodium are harmful, while ammonium salts have little effect, good or bad. Edmunds (1910 and 1911) demonstrated that a milk diet, which contains considerable calcium, with the addition of extra calcium lactate, reduces to a considerable extent the mortality following thyroparathyroidectomy in dogs.

Greenwald (1911) carried out a balanced experiment in which the intake and excretion of nitrogen and phosphate were determined, and he demonstrated retention of phosphorus (the value for serum phosphate was not determined) following thyroparathyroidectomy. Binger in 1917 demonstrated that a solution of ortho-phosphoric acid or its sodium salts the alkalinity of which was more than p_H 6 was definitely toxic if administered intravenously to normal dogs, and produced tetany which was associated with a decrease in the value for the serum calcium. Salvesen (1923), while he was unable to obtain any evidence of the harmful effect of moderate amounts of phosphate, proved what had long been suspected, that the calcium in the milk is the beneficial factor in a milk diet. He demonstrated that when the calcium was removed

by precipitation with oxalate, the milk was no longer beneficial in prolonging the life of parathyroidectomized dogs. Luckhardt and Goldberg (1923) demonstrated that if 10 Gm. of calcium lactate, dissolved or suspended in water, was administered twice a day by means of the stomach tube and if, in addition, 10 Gm. of calcium lactate was mixed with the meat diet, parathyroidectomized dogs usually could be maintained in good condition; however, if calcium phosphate was used, the animals rapidly became worse. Hjort (1925) also demonstrated an important point, namely, that only the soluble salts of calcium are beneficial in the treatment of parathyroidectomized dogs. With the use of a 5 per cent solution of calcium lactate, he demonstrated that the soluble salts are even more efficacious if dissolved in water before administration.

As a result of the curative effect of ultraviolet rays on rickets, as demonstrated by Huldschinssky in 1919, and in latent tetany of infants, as demonstrated by Sachs in 1920 and 1921, Swingle and Rhinhold in 1925 attempted to determine the effects of these rays on parathyroidectomized dogs. The last-mentioned workers demonstrated that if dogs were exposed to ultraviolet rays amelioration of the tetany and prolongation of life occurred as a result of increased absorption and retention of calcium. The value for the calcium in the serum, however, was not materially increased, owing to only a small amount of calcium in the food, as calcium salts were withheld from the standard Cowgill diet. This restriction of calcium salts to a minimum was necessary in most similar experimental work, in order to simplify the problem and to discover the effect, if any, of the experimental substance on the intensity and course of postoperative parathyroid tetany. We wish to emphasize that in the utilization of the results of these experiments by the clinician in an attempt to develop a satisfactory therapeutic procedure such a restriction is not necessary. In fact, in the attempts to determine the effect of cod liver oil, viosterol or parathyroid extract, failure to administer calcium salts has been the basic cause of the poor results of most efforts in the practical treatment of patients who had postoperative parathyroid tetany.

Jones (1926), stimulated by the success of pediatricians in combating rickets and infantile tetany with the use of cod liver oil, studied its effect on the tetany of thyroparathyroidectomized dogs. He found that without the addition of extra calcium salts to the standard diet the administration of 20 cc. of cod liver oil for two weeks before operation prevented tetany and greatly prolonged life. Life was even further prolonged if the cod liver oil was administered continuously both before and after operation. No favorable effect was obtained unless the administration of cod liver oil was started before operation. However, the value for the calcium in the serum of the treated animals decreased

as rapidly and as much as the value for the animals which did not receive cod liver oil, and in some instances more. Some of the dogs which survived longest (from three to six weeks) had symptoms of chronic parathyroid insufficiency, which were of a trophic nature.

Brougher (1928 and 1930) confirmed the observation that when cod liver oil is administered daily to thyroparathyroidectomized dogs which are receiving a large amount of milk (calcium) daily and a little meat (phosphorus) twice a week, the animals do much better than dogs which receive calcium lactate instead of cod liver oil. The value for the calcium in the serum of the dogs which were receiving cod liver oil tended to approach the normal, while that of the dogs which were used as controls or even those which were receiving calcium lactate did not increase. The author carried thyroparathyroidectomized animals through estrus, pregnancy and lactation by the addition of cod liver oil to the stock diet, which contained milk. Wade (1929) also reported definite beneficial effects as a result of the use of cod liver oil. On the other hand, Greenwald and Gross (1925 and 1929) stated that they could not see how the beneficial effects which followed the administration of cod liver oil could be attributed, either in their own experiments or in the experiments of Brougher and Wade, to the cod liver oil itself; they offered many other explanations, the most important of which follows: "The opinion is expressed that the effect of cod liver oil, and the administration of parathyroid extract, upon calcium metabolism will be found to vary with the calcium content of the diet, the age of the animal, and the need for calcium in the organism."

In 1924 it was demonstrated independently by Hess and by Steenbock and Nelson that various foods, such as oils, milk and cereals, can be endowed with specific antirachitic properties by exposure to ultraviolet rays. The next year they demonstrated that the substance which undergoes change is a sterol. Windaus and Hess (1926), Hess (1927), Hess and Windaus (1927) and Rosenheim and Webster demonstrated by chemical analyses and spectral absorption tests that the substance activated is ergosterol (a sterol closely allied to cholesterol), which is extracted from fungi, yeast, mushrooms and ergot. It was quickly recognized that this activated sterol possesses properties similar to those of vitamin D in cod liver oil (Hess and Lewis). However, as can be seen in the reviews of Harris (1932, 1933, 1934 and 1935) and Bills and his associates, it is fairly certain that the concentrate of vitamin D which is obtained from cod liver oil is not the same substance and does not have exactly the same properties in biologic assays with various species as the vitamin D of viosterol. Rygh (1935) presented physical and chemical data indicating that the two substances are different, and he recommended that the term vitamin D should be used to refer specifically to the substance occurring naturally in cod liver oil and the term

vitamin D_2, to the substance which is of vegetable origin and is produced artificially by irradiation of ergosterol. This recommendation has not yet been officially or extensively adopted; in fact, Bills, in a recent review of the multiple nature of vitamin D, stated that there probably are at least six forms of this vitamin. In the United States irradiated ergosterol is known as viosterol.[1] Calciferol is the name of a British preparation of pure crystalline vitamin D; 1 mg. of this preparation is four times as active as crude irradiated ergosterol. Space prohibits a review of the literature on vitamin D, and we can only point out that the difference in the effects of cod liver oil and of viosterol in cases of parathyroid insufficiency may be attributed partially to the fact that the cod liver oil contains vitamin A as well as vitamin D, while viosterol contains only vitamin D in a concentrated form, and partially to the fact that the vitamin D of cod liver oil probably is not identical with the vitamin D_2 of viosterol. Further, the toxic properties of various preparations of irradiated ergosterol varied considerably until recently, because of differences in the methods of irradiation, the length of exposure and other factors.

A preparation of irradiated ergosterol apparently was first used in 1928 in the treatment of postoperative parathyroid tetany in man and experimental animals by Urechia and Popoviciu, who reported a doubtful or slightly beneficial effect, with slight increase in the amount of calcium in the serum of parathyroidectomized dogs. Brougher also reported good results when this substance was administered in conjunction with calcium lactate in the form of milk; he emphasized the necessity of a regular supply of calcium and pointed out that if the dog did not retain the milk, tetany developed. Stern reported a case in which a patient who had had parathyroid insufficiency for fifteen years was markedly improved by the use of a small dose of a German preparation of irradiated ergosterol three times a day. Demole and Christ (1929) confirmed the value of irradiated ergosterol in the control of tetany following thyroparathyroidectomy on dogs.

Hess, Weinstock and Rivkin in 1928 and 1929 suggested that the administration of vitamin D increases the concentration of calcium in the serum by acting on the parathyroid glands, as viosterol did not control the tetany unless it was administered some time before operation. If administration of viosterol was started after removal of the parathyroid glands, tetany developed. In 1930 the authors demonstrated, however, that if large doses (from one to four hundred times the therapeutic dose) of viosterol were administered, hypercalcemia was produced

1. Viosterol is the name used by the American Medical Association Press to designate preparations of irradiated ergosterol (New and Nonofficial Remedies, Chicago, American Medical Association Press, 1935).

in thyroparathyroidectomized dogs. They pointed out that the use of large doses of viosterol may cause withdrawal of calcium from the bones, as shown by Shohl, Bennett and Weed, but that the administration of small amounts brings about retention of calcium, as is true of the use of cod liver oil and of direct ultraviolet irradiation. They therefore withdrew their earlier interpretation that viosterol is effective only when the parathyroid glands are intact.

Reed and Seed (1933) reported on the treatment of ten patients who had postoperative parathyroid tetany with variable but large doses of viosterol and variable but small amounts of calcium lactate or, at times, without calcium. All the patients were benefited, but their condition fluctuated greatly, as illustrated by the variation in the value for calcium, from 6.6 to 14 mg. per hundred cubic centimeters of serum in one instance. These authors concluded that with careful observation a concentrated preparation of viosterol may be safely administered to human subjects in amounts up to 1 cc. daily for several days, without danger of the development of a toxic condition.

The investigations of Higgins and Sheard (1928), Higgins, Sheard and Wilder and Wilder, Higgins and Sheard are important because these investigators demonstrated that in chickens deprivation of vitamin D, in a degree insufficient to cause rickets, produces hypertrophy and hyperplasia of the parathyroid glands. They also referred to the observation of Johnson that the administration of from 5 to 60 minims (0.3 to 4 cc.) of viosterol causes a greater degree of calcification of tissue if large doses of parathyroid extract are administered at the same time. It is evident from the first of these studies that there is a close relationship between the activity of the parathyroid glands and vitamin D and that in the treatment of postoperative parathyroid insufficiency in man one must be cautious in administering parathyroid extract simultaneously with vitamin D, as the effect of toxic doses of one substance is enhanced by the simultaneous action of the other.

Dale, Marble and Marks reported that a British preparation of pure crystalline vitamin D, known as calciferol (1 mg. of which has four times the antirachitic effect of ordinary crude irradiated ergosterol), produces hypervitaminosis. Therefore they concluded that pure vitamin D, whether given in large doses orally or intravenously, has the same characteristic toxic action on dogs as the crude product. They further demonstrated the important fact that complete parathyroidectomy does not prevent or significantly hinder fatal intoxication; at most, it limits the increase in the concentration of calcium to 15 or 17 mg. per hundred cubic centimeters of serum instead of to 18 or 19 mg., which is the concentration produced in the serum of dogs with intact parathyroid glands. The results of these authors lend no support to the suggestion

that administration of vitamin D in excessive doses promotes secretion of parathyroid hormone or renders the organism more responsive to its action.

Other reports appeared on the value of viosterol in the treatment of both experimental and clinical postoperative tetany; in general, more or less benefit was indicated (Jacques; Jones, Rapoport and Hodes and Stacey), while in a few no benefit was reported (Findley). A study of the failures suggests that the unsatisfactory results could usually, but not always, be attributed to one of the following factors: improper dosage, inconsistency of treatment, lack of sufficient readily available calcium in the diet and the presence of calcium, if any, in an insoluble form as the result of excess phosphate or carbonate. Another reason for the conflicting results reported is that viosterol, more than cod liver oil, tends under certain conditions to increase the amount of phosphorus in the serum (Bills, 1935). Harris (1930), Harris and Innes (1931) and Shelling (1932) demonstrated definitely that not only the quantity of calcium in the diet but the ratio of the calcium to the phosphorus is an important factor in the development of hypervitaminosis D with hypercalcemia in normal animals. Shelling (1932) also stated that the calcium and phosphorus content of the diet is important in the treatment of parathyroidectomized rats. The value of diets low in phosphorus and high in calcium in the treatment of parathyroid tetany has been emphasized by Shelling and Goodman (1934), Shelling (1935) and Hoskins.

Holtz and his associates (Holtz, 1927; Holtz and von Brand, 1929; Holtz and Schreiber, 1930, and Holtz, Isemer and Stichnoth, 1931), under the direction of Professor Windaus and his assistants (Windaus and Hess, 1927, and Windaus and Lüttringhaus), were among the first to note that very large doses of vigantol (von Brand and Holtz, 1929 and 1931 and von Brand, Holtz and Putschar), a German preparation of irradiated ergosterol, lead to a series of toxic symptoms which some authors have designated hypervitaminosis D and which consist of nausea, vomiting, hematuria, elevation of blood pressure, increase in the amount of calcium in the serum and the deposition of calcium salts in the heart, blood vessels, kidneys and other organs of the body. Holtz searched for a toxic factor as a possible cause of the hypervitaminosis and found that by prolonging the irradiation of ergosterol under certain conditions he could destroy in large part the antirachitic factor, vitamin D, but that the toxic or "calcinose" factor was still present. Holtz and his associates (Holtz, Laquer, Kreitmair and Moll, 1931, and Holtz, Gissel and Grossmann, 1934) carried out extensive investigations on the action of the "calcinose" factor on normal and parathyroidectomized animals and found that it caused a marked increase in the amount of calcium in the serum of normal animals and a marked deposition of calcium

in the organs of the body; in the parathyroidectomized animals appropriate amounts of this factor increased the value for the serum calcium to normal and prevented the symptoms of parathyroid insufficiency.

Holtz (1933 and 1934) and Holtz, Gürsching and Kraut (1933) announced that a preparation which they called "A. T. 10" (*antitetanisches Präparat Nr. 10*) could be made by the irradiation of ergosterol with a special method. Vitamin D then was removed or destroyed. The remaining mixture of irradiated products was carefully treated, and a purified substance which had a specific effect on calcium metabolism was obtained. They then demonstrated that an extensive series of patients with postoperative parathyroid insufficiency could be treated efficiently with the administration of the proper amount of "A. T. 10." Holtz, however, emphatically warned against the danger of overdosage and stated that if the clinical treatment is not carefully controlled by frequent determinations of the value for serum calcium, serious toxic symptoms develop. In consequence, "A. T. 10" so far has been available only to leading European clinicians for use under carefully controlled conditions (editorial in *Lancet* on Treatment of Tetany, Ekblom, Elliott, Hoff, Martini and Heymer, Marzahn, Paggi, Rieder, Snapper, Wendt and Altenburger, and Winterstein). At present, many reports in the literature fully prove its value in the treatment of postoperative tetany, but on account of the danger of toxic effects and the deposition of calcium salts in various organs, the reports all emphasize that this powerful substance can be used only under close supervision and with frequent determinations of the value for the serum calcium. These favorable results are comparable to those which Boothby and Boothby and Rynearson reported in a series of cases of acute and chronic postoperative parathyroid insufficiency; in this series, which will be referred to later in more detail, the patients were successfully treated with calcium lactate in solution and vitamin D in the form of cod liver oil, and, occasionally, small doses of parathyroid extract were administered.

In 1923 and 1924 Hanson presented evidence indicating that a potent acid extract of the parathyroid gland can be obtained. Collip and his associates, in 1925, describe in detail their method of making an active extract. Such extracts increase the amount of calcium in the serum of normal and parathyroidectomized animals and control the immediate effects of postoperative parathyroid tetany.

Greenwald and Gross demonstrated that the administration of large doses of parathyroid extract leads to excessive solution of calcium phosphate from the bones and to an increase in the concentration of both calcium and phosphate in the serum, and they emphasized Collip's warning against any but the most careful clinical use of parathyroid extract. It should be understood that the hypercalcemia which this extract induces is the result not of improved assimilation but of mobilization of calcium

from the bones, which causes loss of calcium from the body. When this extract was administered to normal dogs in doses of 1 cc., from two to three times a day, there was an increase in the value for the calcium of the serum to 20 mg. per hundred cubic centimeters, and the dogs died in a few days.

Albright, Bauer, Ropes and Curb and Aub found that the administration of parathyroid extract increases the excretion of calcium and phosphorus in human subjects who are receiving a low calcium diet. Bauer, Albright and Aub demonstrated that the prolonged administration of parathyroid extract to cats results in demonstrable decalcification of the bones, and Hunter and Aub found that, in consequence, it is a valuable agent in the treatment of lead poisoning.

The danger of the use of large, and especially of increasing, doses of parathyroid extract in the clinical treatment of postoperative parathyroid tetany is illustrated by the case reported by Lisser and Shepardson, in which the patient died. Shortly after the report of these investigators, Boothby, Haines and Pemberton reported a case in which, for a short time, overdosage of parathyroid extract seemed to lead to the same unfortunate result; they, however, recognized that the low value for the serum calcium, accompanied by tetany, was probably attributable in part to overdosage with parathyroid extract and in part possibly to the failure of the patient to take the calcium lactate and cod liver oil as directed. As already mentioned, the untoward effect of parathyroid extract results from the mobilization of calcium phosphate in the bones and its rapid excretion. After the easily mobilized calcium phosphate has been used up, larger and larger doses of parathyroid extract apparently are needed to produce an appreciable, but temporary, increase in the amount of serum calcium. In consequence, in the case reported by Boothby, Haines and Pemberton the dose of parathyroid extract was reduced from 750 to 125 U.S.P. units daily, and at the same time care was exercised to see that the patient received with certainty each day 30 Gm., in divided doses, of calcium lactate, dissolved in water, with 30 cc. of cod liver oil. The continued administration of calcium lactate and cod liver oil resulted in such marked improvement that the previous harmful effect of large doses of parathyroid extract could not be overlooked, and, conversely, the beneficial effects of calcium lactate and cod liver oil were strikingly evident.

From a consideration of the pertinent facts brought out in this review, the clinical course of tetany following operation on the thyroid gland may be summarized as follows: The complete removal or destruction of the parathyroid glands results in decrease in the total as well as in the ionic concentration of calcium in the blood serum; this is accompanied by gradual increase in the amount of inorganic phosphate in the serum. When the value for the total calcium becomes less than

8 mg. per hundred cubic centimeters of serum, tingling sensations develop in the hands and feet, and as the value for the serum calcium continues to decrease, typical carpopedal contractions develop. If the condition is allowed to go untreated, these contractions may become general and extremely painful and may definitely augment the postoperative risk. If laryngospasm occurs, serious obstruction of the respiratory tract may result and superimpose the additional handicap of anoxemia: In fact, the muscles of the larynx and vocal cords may be among the first to show the effects of spasm, especially if the recurrent laryngeal nerve is irritated by pressure from a ligature or similar cause. If the patient survives the acute attack with adequate treatment and, after leaving the hospital, receives inadequate or intermittent treatment, a series of chronic symptoms develop, while the tetanic-like cramps may become less severe and less frequent as the patient becomes partially adjusted to the decrease in the amount of serum calcium. Occasionally, no evidence of tetany develops while the patient is in the hospital, but the condition first becomes evident a few weeks after operation. Such a delay in the appearance of parathyroid insufficiency can be accounted for on the basis of slight injury by pressure at the time of operation. As a result of chronic parathyroiditis, complete destruction of the parathyroid glands and loss of function occur later, as in the dogs described by Thompson and Leighton. The patient may survive for years, especially if he eats food which contains a moderate amount of calcium and little phosphorus.

The patient with chronic parathyroid insufficiency gradually becomes more incapacitated, and in time trophic changes develop in the teeth, nails and skin. He probably no longer has typical parathyroid tetany, but an epileptiform type of convulsion tends to develop. At times, this may last for hours. The patient is irritable and nervous and becomes so weak that he is virtually helpless. Lenticular opacities are likely to develop. The value for the serum calcium is usually less than 6 mg. and may be less than 5 mg. per hundred cubic centimeters, although occasionally the diet may contain enough calcium and vitamin D to maintain the value for calcium at 7 mg. per hundred cubic centimeters. The value for the inorganic phosphate is high, that is, from 4 to 6 mg., and the value for magnesium is likely to be low, from 1.5 to 1.8 mg. per hundred cubic centimeters of serum. McLean and Hastings and McLean, Barnes and Hastings described an easy method of determining the ionic concentration of calcium in the serum; this method requires the determination of the total protein in grams per hundred cubic centimeters of serum, in addition to the determination of the total amount of calcium in the serum. For practical clinical work, however, determination of the total calcium content of the serum is sufficient for observation of the effect of treatment on postoperative tetany.

In this review also certain facts are emphasized which are of practical value in their applicability to the clinical management of parathyroid insufficiency. The irritability of the neuromuscular system, which results in frequent tetanic spasms, seems to be dependent in the main on a sudden decrease in the amount of calcium in the serum, although there is no close correlation between the spasms and the total or ionic concentration of calcium in the blood serum. The decrease in the amount of calcium in the serum probably is the result of decrease in the absorption of calcium from the gastro-intestinal tract. The administration of vitamin D either as cod liver oil or as viosterol has been shown to be effective in aiding such absorption. The oral administration of the soluble salts of calcium has been shown to be effective, at least temporarily, in preventing actual attacks of tetany by producing an increase in the amount of serum calcium, which lasts for a short time. Calcium salts do not prevent the development of the late trophic disturbances; on the other hand, the simultaneous ingestion of phosphates interferes with the absorption of calcium, as calcium phosphate, which is relatively insoluble, is formed in the intestine. The simultaneous administration of vitamin D and an excess of soluble calcium salts has been shown to be much more effective for a given dose than the administration of either preparation alone. In addition, a diet of moderately low phosphate content should be recommended, such as is obtained by allowing the patient to have meat and yolk of egg, which contain considerable quantities of phosphorus, only once a day. Parathyroid extract does not demonstrably aid absorption of calcium from the gastro-intestinal tract, but it relieves the acute attacks of tetany, at least temporarily, apparently by liberating calcium and phosphate from the bones and thereby increasing the amount of calcium in the serum. This procedure, of course, cannot be continued long without using up the readily mobilized calcium and necessitating larger and larger doses of parathyroid extract, with increasing ineffectiveness. As can be seen from the recent review of Aub, parathyroid extract as it is now made cannot be considered to be the complete hormone of the parathyroid glands, because no one has been able to demonstrate that it fulfils the requirements of complete replacement therapy as does thyroxin for the thyroid gland. Prolonged administration of parathyroid extract, except possibly in very small doses, is distinctly harmful and dangerous in the treatment of chronic parathyroid insufficiency, although, as Aub pointed out, it may occasionally be of value in cases of acute tetany in association with a decrease in the amount of serum calcium. The antitetanic preparation (A. T. 10) which was described by Holtz has proved exceedingly valuable in the treatment of postoperative tetany in cases in which the patient can be closely supervised and the value for the serum calcium determined frequently. Excellent results have been

reported by German investigators; however, they are no better than the effects of treatment which we have obtained at the clinic without the use of this agent.

The therapeutic regimen which most favorably influences the symptoms of postoperative parathyroid insufficiency, recently reported by Boothby and Davis, embraces the following principles: (1) the administration of soluble calcium salts in large doses; (2) the use of a diet low in phosphates; (3) the administration of vitamin D in sufficient amount but in such form that overdosage is unlikely, and (4), finally, the occasional administration of parathyroid extract. On the basis of these principles we have developed a definite method of treating patients with this condition. In some of the cases operation was performed at the clinic and in other instances, elsewhere; therefore the duration of the parathyroid insufficiency varied from a few hours to fifteen years. Patients who have followed instructions and have been able to return for re-examination, observation and slight alteration in their medication have almost invariably done well and have experienced little or no trouble except the necessity of taking calcium lactate, cod liver oil (or viosterol) and, occasionally, small doses of parathyroid extract. The treatment which we have adopted has been designed for the two distinct stages: acute postoperative tetany and chronic parathyroid insufficiency.

The immediate treatment after operation should be instituted as soon as the patient complains of tingling and numbness in the extremities or lips or when the first contraction of the hands develops, with or without accompanying laryngeal spasm. This phase of the treatment is simple and consists in having the patient drink 4 Gm.[2] of powdered calcium lactate dissolved in about a third of a glass of water. This dose should be repeated every half hour until the patient no longer complains of tingling and no longer has spasm. This amount of calcium lactate, always completely dissolved in water, should be given about every two hours throughout the day and once or twice at night, when the patient awakens. The value for the serum calcium should be determined as soon as the tetany is noticed, but one should institute treatment immediately, without awaiting the report.

Occasionally, it may be advisable to give one intravenous injection of 10 cc. of a 10 per cent solution of calcium lactate or calcium gluconate [3] if there has been any delay in recognizing the onset of the tetany or if the patient is in a critical condition. One such injection usually

2. As powdered calcium lactate is light, this amount is equivalent to about two level teaspoonfuls.

3. A 10 per cent solution of calcium chloride is frequently used, but it is dangerous because a few drops escaping into the subcutaneous tissue may cause necrosis of the surrounding tissue.

relieves the spasm, and the oral administration of calcium lactate must then be started immediately. The administration of cod liver oil in doses of from 5 to 10 cc.[4] two or three times daily should be started within twenty-four hours. The continuation of this regimen prevents the development of any symptoms of tetany.

At the end of a week or two, when the patient is entirely out of danger, the administration of calcium and cod liver oil can be discontinued, while the patient is kept under close observation. Frequent estimations of the value for the serum calcium should be made in order to determine whether tetany developed as a result of permanent parathyroid insufficiency or whether the first attack was merely an acute effect of temporary interference with the blood supply of the parathyroid gland.

The treatment for permanent parathyroid insufficiency should be instituted as soon as it is determined that the patient has received irreparable injury of the parathyroid glands. To be satisfactory, the design of such treatment must take into consideration the effectiveness, the cost and the simplicity of application. The treatment necessitates careful and complete instruction of the patient concerning the significance of the situation with which he is faced, as well as the importance of learning and maintaining the regimen outlined.

Of the soluble salts of calcium, calcium lactate is far less expensive than calcium gluconate; it is equally efficacious and should be obtained by the patient in economical quantities. The most highly purified calcium lactate is not necessary, as the presence of a fraction of a per cent of calcium carbonate or even traces of phosphate do no harm; however, the product should not contain appreciable quantities of calcium chloride. The quantity of calcium lactate required in the treatment of tetany varies in the individual case, but usually it is between 20 and 40 Gm. daily. This amount can be measured with sufficient accuracy if one assumes that a level standard tablespoonful contains approximately 5 Gm. The calcium lactate should always be administered in solution, and the patient should be given the following instructions on the preparation of the day's supply: A level tablespoonful of calcium lactate is placed in a suitable dish, and warm water is added slowly while the solution is constantly stirred; then more water and another level tablespoonful of calcium lactate are added, and this procedure is continued until the required daily dose is dissolved and the solution is practically clear. If traces of calcium phosphate or carbonate are present, there is a slight residue, from which the clear solution can be decanted and allowed to cool. The patient should be instructed to take a fifth or sixth of the total daily dose immediately on arising in the morning, a similar amount

4. A teaspoonful of cod liver oil is a little less than 5 cc.

three or four times during the day and a dose on retiring. The dose is more effective if taken a little while before a meal than if taken immediately afterward. A few patients find it necessary to take an extra dose during the night if they become restless or nervous. If the patient is to be away from home, he can take powdered calcium lactate with him and dissolve the proper amount for each individual dose. Nearly all well instructed patients are conscientious about taking the calcium lactate regularly, because they quickly learn to recognize the tingling sensation and nervousness which result from omission of even a few doses.

The regular and constant administration of vitamin D in correct doses is as important as the administration of calcium lactate. It is, however, harder to determine the correct daily dose of vitamin D, and it also is more difficult to impress the patient with the necessity of taking this dose regularly. The ill effects of failure to take vitamin D do not develop quickly, and the patient often can get along for several days or a week or more without experiencing enough discomfort to attract his attention to the omission of the vitamin. Administration of vitamin D seems to be more important in preventing the development of the chronic trophic changes than in preventing the immediate neuromuscular excitability, while the latter condition may be controlled for a considerable time by the administration of calcium lactate. The choice of the form of vitamin D is large and lies between cod liver oil, concentrates of cod liver oil, viosterol and halibut liver oil; however, the commercial combinations of these forms had better not be used except under close supervision. As already mentioned, the fish oils contain vitamin A as well as vitamin D, while viosterol contains only vitamin D. It also has been shown that the vitamin D found in cod liver oil is not identical with the vitamin D (D_2) of viosterol, and it is not yet known for a certainty whether the forms of vitamin D found in the liver oils of various fishes are identical. It has been demonstrated (Bills) that the vitamin D (D_2) of viosterol tends to increase the phosphorus in the serum of an animal relatively more than the vitamin D of cod liver oil when the same degree of protection against rickets is conferred, which probably is undesirable. In spite of the variability of the various preparations of cod liver oil on the market in their absolute and relative contents per gram of vitamin A and vitamin D, we have found it easier to standardize treatment for our patients with cod liver oil than with viosterol. After all, the percentage variability of the vitamin content of the various preparations of cod liver oil accepted by the Council on Pharmacy and Chemistry of the American Medical Association is small as compared to that for viosterol, with its high content of vitamin D and lack of vitamin A. Overdosage of vitamin D is, of course, much more easily obtained accidentally when a concentrated powerful prepara-

tion like viosterol is used. Hypervitaminosis D, with the danger of formation of calcium deposits in various organs, cannot be overlooked. While we have observed one case in which administration of cod liver oil caused mild hypervitaminosis, with nausea and vomiting and an increase in the amount of calcium in the serum to about 13 mg. per hundred cubic centimeters, we have never seen any serious complication arise from its use. Halibut liver oil, which has a much higher concentration of vitamin A and vitamin D than cod liver oil, possibly may be of value in the treatment of postoperative parathyroid insufficiency, especially in cases in which the patient has a distaste for cod liver oil. Its value, however, in the treatment of this condition has not yet been extensively tested. In our experience, administration of from 5 to 10 cc. of cod liver oil two or three times a day usually has proved satisfactory, and if calcium lactate is administered in conjunction, as already described, most patients are maintained in good condition indefinitely. Less cod liver oil apparently is needed in the summer, when the patient is outdoors in the sun more than in the winter. Overdosage with cod liver oil is comparatively easy to recognize rather early, because the patient's distaste for the oil becomes accentuated, with the development of nausea and vomiting; such distaste, however, should be carefully distinguished from the natural dislike of the oily or fishy taste. Other causes for the nausea and vomiting also must be excluded.

If the patient can be kept under observation for a sufficiently long time, the concentrates of cod liver oil can be tried, but often it is not possible to arrange a period of observation which is long enough. We therefore have felt safer in using standard preparations of cod liver oil.

In the cases in which we have made observations recently, we have not found it necessary to use parathyroid extract. In three or four instances, however, in which the intitial treatment consisted of the administration of calcium lactate, cod liver oil and small doses of parathyroid extract, the patients are doing well, or at least reasonably so, and as they cannot return for observation to determine whether the parathyroid extract can be omitted, we have thought it best to suggest no change in the regimen. The amount of parathyroid extract which these patients are taking is comparatively small and does not exceed 0.7 cc. daily (usually less), which is equivalent to 70 U.S.P. units.

The symptoms of myxedema may be associated with those of parathyroid insufficiency and thus may complicate the clinical picture if there has been complete thyroidectomy or if thyroiditis has developed in the remaining thyroid tissue. In our series there were few cases in which there were symptoms of both diseases. If myxedema develops, desiccated thyroid gland should be administered in accordance with the standard method of treating this condition. In the absence of positive

evidence of hypofunction of the thyroid gland, there is, of course, no indication for the administration of desiccated thyroid gland.

Before one undertakes the instruction of a patient in the permanent management of postoperative tetany, the patient and his family should be told that the tetany is the result of unavoidable injury to the parathyroid glands and that if directions are carefully followed no serious result will occur and about the only inconvenience with which the patient must contend is appropriate medication throughout life. Frankness in discussing the condition is due the patient, and it should never lead to legal difficulties which would be upheld in court, as the accident may occur in the hands of the most experienced surgeon, with the exercise of all possible precautions. The parathyroid glands may be situated abnormally far forward and therefore may come into the field of operation. Only rarely can these tiny glands be seen by the surgeon during the operation.

In our experience this treatment is satisfactory in controlling acute parathyroid tetany and in maintaining in health, comfort and usefulness persons with chronic parathyroid insufficiency. Trophic disturbances, such as the progressive development of lenticular opacities, can be controlled, and in some instances at least improvement occurs. Boothby and Lillie reported a case of chronic parathyroid insufficiency with the development of cataracts, in which, in addition to the usual general improvement, marked increase in visual acuity followed the institution of treatment. Subsequently, the patient discontinued the use of vitamin D because he was of the opinion that it increased his weight, but he continued to take the calcium lactate and small doses of parathyroid extract. After the omission of vitamin D the opacities of the lenses markedly increased. No change was made in treatment, except to insist that the patient consistently take two teaspoonfuls of cod liver oil three times a day. In a year vision was again so improved that he could see to drive his car and enjoy motion-pictures, which he had not been able to do before the institution of treatment.

Recently Boothby and Woltman reported a case of chronic parathyroid insufficiency which provided a convincing demonstration of the effect of treatment on the trophic changes that occur in association with the disease, as well as of the control of the nervous irritability. A summary of the case follows:

> A woman, aged 34, primarily complained of the frequent occurrence of cramps in the hands and occasional generalized convulsive seizures, which had gradually increased in severity since she had undergone thyroidectomy eighteen years before. The convulsive seizures had become much more noticeable during the five months prior to admission to the clinic. In addition, there was marked dystrophy of the nails; the Chvostek and Trousseau signs were present, and the patient suffered from marked weakness and nervousness, so that she was completely incapacitated.

The value for the calcium of the serum was 4.3 mg., and that for the phosphate, 5.6 mg., per hundred cubic centimeters of serum. After the institution of treatment, which consisted of the administration of 4 Gm. of calcium lactate dissolved in water eight times daily and 5 cc. of cod liver oil three times daily, there was immediate and striking improvement in the patient's condition. She recovered strength rapidly and in a few days was able to walk for a considerable distance without difficulty. Ten days later the value for the serum calcium increased to 13 mg. per hundred cubic centimeters, and the value for the serum phosphate decreased to 2 mg. The value for the serum calcium decreased immediately after a slight reduction in the amount of calcium lactate and cod liver oil administered daily. When the patient was dismissed, after a month's treatment, the value for the serum calcium was 10.5 mg., and that for the serum phosphate, 3.5 mg., per hundred cubic centimeters. The hypercalcemia was attributed to the fact that larger amounts both of calcium lactate and of cod liver oil are necessary to bring the condition quickly under control, and as soon as this is accomplished and part of the body's depleted calcium is restored, smaller doses of calcium lactate and cod liver oil are sufficient to maintain a calcium balance. When the patient was seen five months later, she was in excellent health and had had no evidence of tetany or chronic parathyroid insufficiency during this interval. The value for the serum calcium was normal, indicating that the amount of calcium lacate and cod liver oil the patient had been consistently taking was the correct amount for this person. The atrophic nails had been shed and were being replaced by healthy ones. For the first time since the development of the symptoms of chronic parathyroid insufficiency, she was leading a normal life and was able to perform the duties of a farmer's wife.

In concluding this review we call attention to the promising results of Stone, Owings and Gey in the transplantation of thyroid and parathyroid glands. These investigators adopted the novel idea of implanting grafts of cultures of thyroid or parathyroid tissue grown on artificial mediums to which increasing quantities of the body fluids of the future host were added. It is to be hoped that this method of transplantation will solve the difficulties hitherto encountered in attempts at grafting. Of special interest to the surgeon is the recent anatomic description by Herrman of the parathyroid glands and their relationship to the parathyroid arteries and the hitherto undescribed parathyroid nerves. The inferior parathyroid nerve is a branch of the recurrent laryngeal nerve, and the superior parathyroid nerve arises from the external division of the superior laryngeal branch of the vagus nerve. Both these nerves join the corresponding parathyroid arteries and with them enter the hilus of the parathyroid gland.

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News and Comment

CHICAGO SOCIETY OF INTERNAL MEDICINE

At the annual meeting of the Chicago Society of Internal Medicine held on May 25 the following officers were elected: president, Dr. Walter L. Palmer; vice president, Dr. Andrew C. Ivy; secretary-treasurer, Dr. Clarence F. G. Brown.

FIFTEENTH ANNUAL SESSION OF AMERICAN CONGRESS OF PHYSICAL THERAPY

The fifteenth annual clinical and scientific session of the American Congress of Physical Therapy will be held on September 7 to 11, at the Waldorf-Astoria Hotel, New York. The program includes many special features: sectional meetings in the specialties, symposia on short wave diathermy, hydrotherapy, exercise and electroresection. Fever therapy and the treatment of vascular diseases occupy an important place and will be discussed by prominent workers in the field. The educational aspects of physical therapy and the relationship of physical therapy technicians to physicians and hospital departments will be thoroughly dealt with. Other features include technical and scientific exhibits and a full day of visiting clinics of hospitals, where technic will be adequately demonstrated.

Physicians, their technical assistants and nurses working in institutional departments of physical therapy are urged to attend this important session. It undoubtedly will be one of the outstanding medical gatherings of the year. There will be no registration fee.

Book Reviews

Examination of the Patient and Symptomatic Diagnosis. By John Watts Murray, M.D. Second edition. Price $10. Pp. 1,219, with 274 illustrations. St. Louis: C. V. Mosby Company, 1936.

From time to time attempts are made to simplify the procedure of diagnosis by offering one or another variety of formulary. One is told to consult a list of symptoms, obtains cross-references to various pages and finally by an almost automatic procedure learns what ails any particular patient. That such a system can ever work, that formulas can ever replace knowledge of disease and clinical reasoning, is a proposition too absurd to require any particular challenge.

In the present book the author attempts to simplify diagnosis along these lines. Under each organ, the stomach for example, are a great number of questions and answers, such as: "Pain at McBurney's point? Appendicitis;" or "Has the patient suffered from recurring attacks of pain over a length of time, with intervals of entire relief between the attacks? Answer: Chronic periodic gastro-succorrhoea of the primary or secondary form." One need hardly go farther to make clear the futility of such a compendium; indeed "we recall no equal quantity of printed matter which has pleased us less."

Verhandlungen der deutschen Gesellschaft für Kreislaufforschung VIII Tagung. By Prof. Dr. E. Koch. Price, 15 marks. Pp. 262, with 80 illustrations. Dresden: Theodor Steinkopff, 1935.

This volume contains the transactions of the German Society for the Investigation of Circulatory Disease for 1935. The main topic for discussion was the relation of circulation and respiration. A long series of interesting articles are included, many of them containing original material, and such names as Wenckebach and Hochrein indicate the caliber of the speakers. The volume is handsomely published, with many illustrations.

Normale und pathologische Physiologie der Bewegungsvorgänge im gesamten Verdauungskanal: Teil 1. Methodik, Anatomie, normale Physiologie. By Prof. Dr. Med. Werner Catel. Paper. Price, 11.50 marks. Pp. 250, with illustrations. Leipzig: Georg Thieme, 1936.

This book details in monographic form about all that is known in regard to the motility of the gastro-intestinal tract. Methods of study, both experimental and clinical, are detailed, with a large collection of excellent diagrams and illustrations.

Blutungskrankheiten. By Dr. Heinrich Lehndorff. Price, 3.30 marks. Pp. 75. Berlin: Julius Springer, 1935.

This is one of a series of little books for general practitioners. The subject of hemorrhagic disease, which at best is difficult, is dealt with briefly but in accord with modern views.